NEW PYRIDAZIN-3(2*H*)-ONE DERIVATIVES

The present invention relates to new therapeutically useful pyridazin-3(2*H*)-one derivatives, to processes for their preparation and to pharmaceutical compositions containing them. These compounds are potent and selective inhibitors of phosphodiesterase 4 (PDE4) and are thus useful in the treatment, prevention or suppression of pathological conditions, diseases and disorders known to be susceptible of being improved by inhibition of PDE4.

Phosphodiesterases (PDEs) comprise a superfamily of enzymes responsible for the hydrolysis and inactivation of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Eleven different PDE families have been identified to date (PDE1 to PDE11) which differ in substrate preference, catalytic activity, sensitivity to endogenous activators and inhibitors, and encoding genes.

The PDE4 isoenzyme family exhibits a high affinity for cyclic AMP but has weak affinity for cyclic GMP. Increased cyclic AMP levels caused by PDE4 inhibition are associated with the suppression of cell activation in a wide range of inflammatory and immune cells, including lymphocytes, macrophages, basophils, neutrophils, and eosinophils. Moreover, PDE4 inhibition decreases the release of the cytokine Tumor Necrosis Factor α (TNFα). The biology of PDE4 is described in several recent reviews, for example M. D. Houslay, *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, *69*, 249-315; J. E. Souness et al. *Immunopharmacol.* **2000** *47*, 127-162; or M. Conti and S. L. Jin, *Prog. Nucleic Acid Res. Mol. Biol.* **1999**, *63*, 1-38.

In view of these physiological effects, PDE4 inhibitors of varied chemical structures have been recentlty disclosed for the treatment or prevention of chronic and acute inflammatory diseases and of other pathological conditions, diseases and disorders known to be susceptible to amelioration by inhibition of PDE4. See, for example, US 5449686, US 5710170, WO 98/45268, WO 99/06404, WO 01/57025, WO 01/57036, WO 01/46184, WO 97/05105, WO 96/40636, US 5786354, US 5773467, US 5753666, US 5728712, US 5693659, US 5679696, US 5596013, US 5541219, US 5508300, US 5502072 or H. J. Dyke and J. G. Montana, *Exp. Opin. Invest. Drugs* **1999**, *8*, 1301-1325.

A few compounds having the capacity to selectively inhibit phosphodiesterase 4 are in active development. Examples of these compounds are cipamfylline (European Patent number 0 389 282 B1), arofyline (European patent number 0 435 811 B1), cilomilast, roflumilast (European Patent number 0 706 513 B1), mesopram (European Patent number 0 859 766 B1) and pumafentrine (PCT Patent application number 98/21208 A1).

We have now found that a novel series of pyridazin-3(2*H*)-one derivatives are potent and selective inhibitors of PDE4 and are therefore useful in the treatment or prevention of these pathological conditions, diseases and disorders, in particular asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

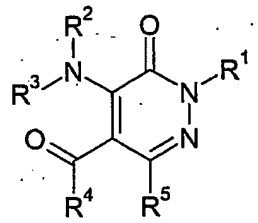
The compounds of the present invention can also be used in combination with other drugs known to be effective in the treatment of these diseases. For example, they can be used in combination with steroids or immunosuppressive agents, such as cyclosporin A, rapamycin or T-cell receptor blockers. In this case the administration of the compounds allows a reduction of the dosage of the other drugs, thus preventing the appearance of the undesired side effects associated with both steroids and immunosuppressants.

Like other PDE4 inhibitors (see references above) the compounds of the invention can also be used for blocking the ulcerogenic effects induced by a variety of etiological agents, such as antiinflammatory drugs (steroidal or non-steroidal antiinflammatory agents), stress, ammonia, ethanol and concentrated acids. They can be used alone or in combination with antacids and/or antisecretory drugs in the preventive and/or curative treatment of gastrointestinal pathologies like drug-induced ulcers, peptic ulcers, H. Pylori-related ulcers, esophagitis and gastro-esophageal reflux disease.

They can also be used in the treatment of pathological situations where damage to the cells or tissues is produced through conditions like anoxia or the production of an excess of free radicals. Examples of such beneficial effects are the protection of cardiac tissue after coronary artery occlusion or the prolongation of cell and tissue viability when the compounds of the invention are added to preserving solutions

intended for storage of transplant organs or fluids such as blood or sperm. They are also of benefit on tissue repair and wound healing.

Accordingly, the present invention provides novel compounds of formula (I):



(I)

wherein

R^1 and R^2 represent independently from each other:

- a hydrogen atom;
- a group selected from acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, monoalkylcarbamoyl or dialkylcarbamoyl;
- an alkyl, alkenyl or alkynyl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, carbamoyl, mono- or di-alkylcarbamoyl groups;
- an aryl or heteroaryl group which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, hydroxyalkyl, hydroxycarbonyl, alkoxy, alkylenedioxy, alkoxyacyl, aryloxy, acyl, acyloxy, alkylthio, amino, nitro, cyano, mono- or di-alkylamino, acylamino, carbamoyl, mono- or di-alkylcarbamoyl, difluoromethyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups;
- a saturated or unsaturated heterocyclic group which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, hydroxyalkyl, hydroxycarbonyl, alkoxy, alkylenedioxy, alkoxyacyl, aryloxy, acyl, acyloxy, alkylthio, oxo, amino, nitro, cyano, mono- or di-alkylamino, acylamino, carbamoyl, mono- or di-alkylcarbamoyl, difluoromethyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups;
- a group of formula

$$-(CH_2)_n-R^6$$

wherein n is an integer from 0 to 4 and R^6 represents:

- a cycloalkyl or cycloalkenyl group;
- an aryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy, alkylthio, amino, mono- or di-alkylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, cyano, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups;
- or a 3- to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy, amino, mono- or di-alkylamino, nitro, cyano or trifluoromethyl groups;

R^3 represents a monocyclic or polycyclic aryl or heteroaryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from:

- halogen atoms;
- alkyl and alkylene groups, which are optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms; and phenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl groups
- phenyl, hydroxy, hydroxyalkyl, alkoxy, cycloalkoxy, nitro, aryloxy, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphamoyl, acyl, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulphamido, aminosuphonyl, mono- or di-alkylaminosulphonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

R^5 represents a group $-COOR^7$ or a monocyclic or polycyclic aryl or heteroaryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and phenyl,

hydroxy, hydroxyalkyl, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl groups; y

- phenyl, hydroxy, alkylenedioxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulfamoyl, amino, mono- or di-alkylamino, acylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulphamido, aminosuphonyl, mono- or di-alkylaminosulphonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

wherein R^7 represents an alkyl group which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl and mono- or di-alkylcarbamoyl groups or a group of formula:

$$-(CH_2)_n-R^6$$

wherein n and R^6 are as defined above, and

R^4 represents:

- a hydrogen atom;
- a hydroxy, alkoxy, amino, mono- or di-alkylamino group;
- an alkyl, alkenyl or alkynyl group which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl and mono- or di-alkylcarbamoyl groups;
- or a group of formula

$$-(CH_2)_n-R^6$$

wherein n and R^6 are as defined above.

as well as the N-oxides obtainable from the heteroaryl radicals present in the structure when these heteroradicals comprise N atoms and pharmaceutically acceptable salts thereof,

with the proviso that when R^5 is neither an optionally substituted heteroaryl group nor a group $COOR^7$, then R^3 is an optionally substituted heteroaryl group.

Certain pyridazin-3(2*H*)-one derivatives of similar structure, which do not fall within the scope of the present invention, have been disclosed in *J. Pharm. Sci.* **1991**, *80*, 341-348 and *J. Med. Chem.* **1999**, *42*, 1894-1900.

Further objectives of the present invention are to provide processes for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by inhibition of PDE4; and methods of treatment of diseases susceptible to amelioration by inhibition of PDE4, which methods comprise the administration of the compounds of the invention to a subject in need of treatment.

As used herein the term alkyl embraces optionally substituted, linear or branched radicals having 1 to 20 carbon atoms or, preferably 1 to 12 carbon atoms. More preferably alkyl radicals are "lower alkyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, n-hexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl and iso-hexyl radicals.

As used herein, the term alkenyl embraces optionally substituted, linear or branched, mono or polyunsaturated radicals having 1 to 20 carbon atoms or, preferably, 1 to 12 carbon atoms. More preferably alkenyl radicals are "lower alkenyl" radicals having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms. In particular it is preferred that the alkenyl radicals are mono or diunsaturated.

Examples include vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl and 4-pentenyl radicals.

As used herein, the term alkynyl embraces optionally substituted, linear or branched, mono or polyunsaturated radicals having 1 to 20 carbon atoms or, preferably, 1 to 12 carbon atoms. More preferably, alkynyl radicals are "lower alkynyl" radicals having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms. In particular, it is preferred that the alkynyl radicals are mono or diunsaturated.

Examples include 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl radicals.

When it is mentioned that alkyl, alkenyl or alkynyl radicals may be optionally subsituted it is meant to include linear or branched alkyl, alkenyl or alkynyl radicals as defined above, which may be unsubstituted or substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different.

A said optionally substituted alkenyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkenyl group are themselves unsubstituted.

A said optionally substituted alkynyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkynyl group are themselves unsubstituted.

A said optionally substituted alkyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkyl group are

themselves unsubstituted. Preferred optionally substituted alkyl groups are unsubstituted or substituted with 1, 2 or 3 fluorine atoms.

As used herein, the term alkylene embraces divalent alkyl moieties typically having from 1 to 6, for example from 1 to 4, carbon atoms. Examples of C_1-C_4 alkylene radicals include methylene, ethylene, propylene, butylene, pentylene and hexylene radicals.

A said optionally substituted alkylene group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms.

When an alkylene radical is present as a substituent on another radical it shall be deemed to be a single substituent, rather than a radical formed by two substituents.

As used herein, the term alkoxy (or alkyloxy) embraces optionally substituted, linear or branched oxy-containing radicals each having alkyl portions of 1 to 10 carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkoxy group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkoxy group are themselves unsubstituted.

Preferred alkoxy radicals include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy and 2-hydroxypropoxy.

As used herein, the term alkylthio embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkylthio group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkythio group are themselves unsubstituted.

Preferred optionally substituted alkylthio radicals include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, sec-butylthio, t-butylthio, trifluoromethylthio, difluoromethylthio, hydroxymethylthio, 2-hydroxyethylthio and 2-hydroxypropylthio.

As used herein, the term monoalkylamino embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent –NH- radical. More preferred monoalkylamino radicals are "lower monoalkylamino" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

A monoalkylamino group typically contains an alkyl group which is unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substitutents on a monoalkylamino group are themselves unsubstituted.

Preferred optionally substituted monoalkylamino radicals include methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, sec-butylamino, t-butylamino, trifluoromethylamino, difluoromethylamino, hydroxymethylamino, 2-hydroxyethylamino and 2-hydroxypropylamino.

As used herein, the term dialkylamino embraces radicals containing a trivalent nitrogen atoms with two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached thereto. More preferred dialkylamino radicals are "lower dialkylamino" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

A dialkylamino group typically contains two alkyl groups, each of which is unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a dialkylamino group are themselves unsubstituted.

Preferred optionally substituted dialkylamino radicals include dimethylamino, diethylamino, methyl(ethyl)amino, di(n-propyl)amino, n-propyl(methyl)amino, n-propyl(ethyl)amino, di(i-propyl)amino, i-propyl(methyl)amino, i-propyl(ethyl)amino, di(n-butyl)amino, n-butyl(methyl)amino, n-butyl(ethyl)amino, n-butyl(i-propyl)amino, di(sec-butyl)amino, sec-butyl(methyl)amino, sec-butyl(ethyl)amino, sec-butyl(n-propyl)amino, sec-butyl(i-propyl)amino, di(t-butyl)amino, t-butyl(methyl)amino, t-butyl(ethyl)amino, t-butyl(n-propyl)amino, t-butyl(i-propyl)amino, trifluoromethyl(methyl)amino, trifluoromethyl(ethyl)amino, trifluoromethyl(n-propyl)amino, trifluoromethyl(i-propyl)amino, trifluoromethyl(n-butyl)amino, trifluoromethyl(sec-butyl)amino, difluoromethyl(methyl)amino, difluoromethyl(ethyl)amino, difluoromethyl(n-propyl)amino, difluoromethyl(i-propyl)amino, difluoromethyl(n-butyl))amino, difluoromethyl(sec-butyl)amino, difluoromethyl(t-butyl)amino, difluoromethyl(trifluoromethyl)amino, hydroxymethyl(methyl)amino, ethyl(hydroxymethyl)amino, hydroxymethyl(n-propyl)amino, hydroxymethyl(i-propyl)amino, n-butyl(hydroxymethyl)amino, sec-butyl(hydroxymethyl)amino, t-butyl(hydroxymethyl)amino, difluoromethyl(hydroxymethyl)amino, hydroxymethyl(trifluoromethyl)amino, hydroxyethyl(methyl)amino, ethyl(hydroxyethyl)amino, hydroxyethyl(n-propyl)amino, hydroxyethyl(i-propyl)amino, n-butyl(hydroxyethyl)amino, sec-butyl(hydroxyethyl)amino, t-butyl(hydroxyethyl)amino, difluoromethyl(hydroxyethyl)amino, hydroxyethyl(trifluoromethyl)amino, hydroxypropyl(methyl)amino, ethyl(hydroxypropyl)amino, hydroxypropyl(n-propyl)amino, hydroxypropyl(i-propyl)amino, n-butyl(hydroxypropyl)amino, sec-butyl(hydroxypropyl)amino, t-butyl(hydroxypropyl)amino, difluoromethyl(hydroxypropyl)amino, hydroxypropyl(trifluoromethyl)amino.

As used herein, the term hydroxyalkyl embraces linear or branched alkyl radicals having 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals.

Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

As used herein, the term alkoxycarbonyl embraces optionally substituted, linear or branched radicals each having alkyl portions of 1 to 10 carbon atoms and attached to an oxycarbonyl radical. More preferred alkoxycarbonyl radicals are "lower alkoxycarbonyl" radicals, in which the alkyl moiety has 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkoxycarbonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkoxycarbonyl group are themselves unsubstituted.

Preferred optionally substituted alkoxycarbonyl radicals include methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, trifluoromethoxycarbonyl, difluoromethoxycarbonyl, hydroxymethoxycarbonyl, 2-hydroxyethoxycarbonyl and 2-hydroxypropoxycarbonyl.

As used herein, the term monoalkylcarbamoyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms and attached to the nitrogen of a–NHCO- radical. More preferred monoalkylcarbamoyl radicals are "lower monoalkylcarbamoyl" radicals in which the alkyl moiety has 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

A monoalkylcarbamoyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylcarbamoyl group are themselves unsubstituted.

Preferred optionally substituted monoalkylcarbamoyl radicals include methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, i-propylcarbamoyl, n-butylcarbamoyl, sec-

butylcarbamoyl, t-butylcarbamoyl, trifluoromethylcarbamoyl, difluoromethylcarbamoyl, hydroxymethylcarbamoyl, 2-hydroxyethylcarbamoyl and 2-hydroxypropylcarbamoyl.

As used herein, the term dialkylcarbamoyl embraces radicals containing a radical NCO- where the nitrogen is attached to two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms. More preferred dialkylcarbamoyl radicals are "lower dialkylcarbamoyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

A dialkylcarbamoyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a dialkylcarbamoyl group are themselves unsubstituted.

Preferred optionally substituted dialkylcarbamoyl radicals include dimethylcarbamoyl, diethylcarbamoyl, methyl(ethyl)carbamoyl, di(n-propyl)carbamoyl, n-propyl(methyl)carbamoyl, n-propyl(ethyl)carbamoyl, di(i-propyl)carbamoyl, i-propyl(methyl)carbamoyl, i-propyl(ethyl)carbamoyl, di(n-butyl)carbamoyl, n-butyl(methyl)carbamoyl, n-butyl(ethyl)carbamoyl, n-butyl(i-propyl)carbamoyl, di(sec-butyl)carbamoyl, sec-butyl(methyl)carbamoyl, sec-butyl(ethyl)carbamoyl, sec-butyl(n-propyl)carbamoyl, sec-butyl(i-propyl)carbamoyl, di(t-butyl)carbamoyl, t-butyl(methyl)carbamoyl, t-butyl(ethyl)carbamoyl, t-butyl(n-propyl)carbamoyl, t-butyl(i-propyl)carbamoyl, trifluoromethyl(methyl)carbamoyl, trifluoromethyl(ethyl)carbamoyl, trifluoromethyl(n-propyl)carbamoyl, trifluoromethyl(i-propyl)carbamoyl, trifluoromethyl(n-butyl)carbamoyl, trifluoromethyl(sec-butyl)carbamoyl, difluoromethyl(methyl)carbamoyl, difluoromethyl(ethyl)carbamoyl, difluoromethyl(n-propyl)carbamoyl, difluoromethyl(i-propyl)carbamoyl, difluoromethyl(n-butyl))carbamoyl, difluoromethyl(sec-butyl)carbamoyl, difluoromethyl(t-butyl)carbamoyl, difluoromethyl(trifluoromethyl)carbamoyl, hydroxymethyl(methyl)carbamoyl, ethyl(hydroxymethyl)carbamoyl, hydroxymethyl(n-propyl)carbamoyl, hydroxymethyl(i-propyl)carbamoyl, n-butyl(hydroxymethyl)carbamoyl, sec-butyl(hydroxymethyl)carbamoyl, t-butyl(hydroxymethyl)carbamoyl, difluoromethyl(hydroxymethyl)carbamoyl, hydroxymethyl(trifluoromethyl)carbamoyl, hydroxyethyl(methyl)carbamoyl, ethyl(hydroxyethyl)carbamoyl, hydroxyethyl(n-

propyl)carbamoyl, hydroxyethyl(i-propyl)carbamoyl, n-butyl(hydroxyethyl)carbamoyl, sec-butyl(hydroxyethyl)carbamoyl, t-butyl(hydroxyethyl)carbamoyl, difluoromethyl(hydroxyethyl)carbamoyl, hydroxyethyl(trifluoromethyl)carbamoyl, hydroxypropyl(methyl)carbamoyl, ethyl(hydroxypropyl)carbamoyl, hydroxypropyl(n-propyl)carbamoyl, hydroxypropyl(i-propyl)carbamoyl, n-butyl(hydroxypropyl)carbamoyl, sec-butyl(hydroxypropyl)carbamoyl, t-butyl(hydroxypropyl)carbamoyl, difluoromethyl(hydroxypropyl)carbamoyl, hydroxypropyl(trifluoromethyl)carbamoyl.

As used herein, the term alkylsulfinyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent –SO- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkylsulfinyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a alkylsulfinyl group are themselves unsubstituted.

Preferred optionally substituted alkylsulphinyl radicals include methylsulphinyl, ethylsulphinyl, n-propylsulphinyl, i-propylsulphinyl, n-butylsulphinyl, sec-butylsulphinyl, t-butylsulphinyl, trifluoromethylsulphinyl, difluoromethylsulphinyl, hydroxymethylsulphinyl, 2-hydroxyethylsulphinyl and 2-hydroxypropylsulphinyl.

As used herein, the term alkylsulfonyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent $-SO_2-$ radical. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkylsulfonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylaminosulfonyl group are themselves unsubstituted.

As used herein, the term monoalkylaminosulfonyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms and attached to the nitrogen of a–$NHSO_2$- radical. More preferred monoalkylaminosulfonyl radicals are "lower monoalkylaminosulfonyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

A monoalkylaminosulfonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylaminosulfonyl group are themselves unsubstituted.

Preferred optionally substituted monoalkylaminosulphonyl radicals include methylaminosulphonyl, ethylaminosulphonyl, n-propylaminosulphonyl, i-propylaminosulphonyl, n-butylaminosulphonyl, sec-butylaminosulphonyl, t-butylaminosulphonyl, trifluoromethylaminosulphonyl, difluoromethylaminosulphonyl, hydroxymethylaminosulphonyl, 2-hydroxyethylaminosulphonyl and 2-hydroxypropylaminosulphonyl.

As used herein, the term dialkylaminosulfonyl embraces radicals containing a radical NSO_2- where the nitrogen is attached to two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms. More preferred dialkylaminosulfonyl radicals are "lower dialkylaminosulfonyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

A dialkylaminosulfonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a dialkylaminosulphonyl group are themselves unsubstituted.

Preferred optionally substituted dialkylaminosulphonyl radicals include dimethylaminosulphonyl, diethylaminosulphonyl, methyl(ethyl)aminosulphonyl, di(n-propyl)aminosulphonyl, n-propyl(methyl)aminosulphonyl, n-propyl(ethyl)aminosulphonyl, di(i-propyl)aminosulphonyl, i-

propyl(methyl)aminosulphonyl, i-propyl(ethyl)aminosulphonyl, di(n-butyl)aminosulphonyl, n-butyl(methyl)aminosulphonyl, n-butyl(ethyl)aminosulphonyl, n-butyl(i-propyl)aminosulphonyl, di(sec-butyl)aminosulphonyl, sec-butyl(methyl)aminosulphonyl, sec-butyl(ethyl)aminosulphonyl, sec-butyl(n-propyl)aminosulphonyl, sec-butyl(i-propyl)aminosulphonyl, di(t-butyl)aminosulphonyl, t-butyl(methyl)aminosulphonyl, t-butyl(ethyl)aminosulphonyl, t-butyl(n-propyl)aminosulphonyl, t-butyl(i-propyl)aminosulphonyl, trifluoromethyl(methyl)aminosulphonyl, trifluoromethyl(ethyl)aminosulphonyl, trifluoromethyl(n-propyl)aminosulphonyl, trifluoromethyl(i-propyl)aminosulphonyl, trifluoromethyl(n-butyl)aminosulphonyl, trifluoromethyl(sec-butyl)aminosulphonyl, difluoromethyl(methyl)aminosulphonyl, difluoromethyl(ethyl)aminosulphonyl, difluoromethyl(n-propyl)aminosulphonyl, difluoromethyl(i-propyl)aminosulphonyl, difluoromethyl(n-butyl))aminosulphonyl, difluoromethyl(sec-butyl)aminosulphonyl, difluoromethyl(t-butyl)aminosulphonyl, difluoromethyl(trifluoromethyl)aminosulphonyl, hydroxymethyl(methyl)aminosulphonyl, ethyl(hydroxymethyl)aminosulphonyl, hydroxymethyl(n-propyl)aminosulphonyl, hydroxymethyl(i-propyl)aminosulphonyl, n-butyl(hydroxymethyl)aminosulphonyl, sec-butyl(hydroxymethyl)aminosulphonyl, t-butyl(hydroxymethyl)aminosulphonyl, difluoromethyl(hydroxymethyl)aminosulphonyl, hydroxymethyl(trifluoromethyl)aminosulphonyl, hydroxyethyl(methyl)aminosulphonyl, ethyl(hydroxyethyl)aminosulphonyl, hydroxyethyl(n-propyl)aminosulphonyl, hydroxyethyl(i-propyl)aminosulphonyl, n-butyl(hydroxyethyl)aminosulphonyl, sec-butyl(hydroxyethyl)aminosulphonyl, t-butyl(hydroxyethyl)aminosulphonyl, difluoromethyl(hydroxyethyl)aminosulphonyl, hydroxyethyl(trifluoromethyl)aminosulphonyl, hydroxypropyl(methyl)aminosulphonyl, ethyl(hydroxypropyl)aminosulphonyl, hydroxypropyl(n-propyl)aminosulphonyl, hydroxypropyl(i-propyl)aminosulphonyl, n-butyl(hydroxypropyl)aminosulphonyl, sec-butyl(hydroxypropyl)aminosulphonyl, t-butyl(hydroxypropyl)aminosulphonyl, difluoromethyl(hydroxypropyl)aminosulphonyland hydroxypropyl(trifluoromethyl)aminosulphonyl.

As used herein, the term alkylsulfamoyl embraces radicals containing an optionally substituted, linear or branched alkyl radical of 1 to 10 carbon atoms and attached to the nitrogen of a–NSO_2- radical. More preferred alkylsulfamoyl radicals are "lower alkylsulfamoyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkylsulphamoyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkylsulphamoyl group are themselves unsubstituted.

Preferred optionally substituted alkylsulfamoyl radicals include methylsulphamoyl, ethylsulphamoyl, n-propylsulphamoyl, i-propylsulphamoyl, n-butylsulphamoyl, sec-butylsulphamoyl, t-butylsulphamoyl, trifluoromethylsulphamoyl, difluoromethylsulphamoyl, hydroxymethylsulphamoyl, 2-hydroxyethylsulphamoyl and 2-hydroxypropylsulphamoyl.

As used herein, the term alkylsulphamido embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms and attached to one of the nitrogen atoms of a $-NHSO_2NH-$ radical. More preferred alkylsulphamido radicals are "lower alkylsulphamido" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkylsulphamido group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkylsulphamido group are themselves unsubstituted.

Preferred optionally substituted alkylsulphamido radicals include methylsulphamido, ethylsulphamido, n-propylsulphamido, i-propylsulphamido, n-butylsulphamido, sec-butylsulphamido, t-butylsulphamido, trifluoromethylsulphamido, difluoromethylsulphamido, hydroxymethylsulphamido, 2-hydroxyethylsulphamido and 2-hydroxysulphamido.

As used herein, the term N'-alkylureido embraces radicals containing an optionally substituted, linear or branched alkyl radical of 1 to 10 carbon atoms attached to the terminal nitrogen of a $-NHCONH-$ radical. More preferred N'-alkylureido radicals are

"lower N'-alkylureido" radicals in which the alkyl moiety has 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An N'-alkylureido group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an N'-alkylureido group are themselves unsubstituted.

Preferred optionally substituted N'-alkylureido radicals include N'-methylureido, N'-ethylureido, N'-n-propylureido, N'-i-propylureido, N'-n-butylureido, N'-sec-butylureido, N'-t-butylureido, N'-trifluoromethylureido, N'-difluoromethylureido, N'-hydroxymethylureido, N'-2-hydroxyethylureido and N'-2-hydroxypropylureido.

As used herein, the term N',N'-dialkylureido embraces radicals containing a radical –NHCON– where the terminal nitrogen is attached to two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms. More preferred N',N'-dialkylureido radicals are "lower N',N'-dialkylureido" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

A N',N'-dialkylureido group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an N',N'-dialkylureido group are themselves unsubstituted.

Preferred optionally substituted N',N'-dialkylureido radicals include N',N'-dimethylureido, N',N'-diethylureido, N'-methyl,N'-ethylureido, N',N'-di(n-propyl)ureido, N'-n-propyl,N'-methylureido, N'-n-propyl,N'-ethylureido, N',N'-di(i-propyl)ureido, N'-i-propyl,N'-methylureido, N'-i-propyl,N'-ethylureido, N',N'-di(n-butyl)ureido, N'-n-butyl,N'-methylureido, N'-n-butyl,N'-ethylureido, N'-n-butyl,N'-(i-propyl)ureido, N',N'-di(sec-butyl)ureido, N'-sec-butyl,N'-methylureido, N'-sec-butyl,N'-ethylureido, N'-sec-butyl,N'-(n-propyl)ureido, N'-sec-butyl,N'(i-propyl) ureido, N',N'di(t-butyl)ureido, N'-t-butyl,N'-methylureido, N'-t-butyl,N'-ethylureido, N'-t-butyl,N'-(n-propyl)ureido, N'-t-butyl,N'-(i-propyl)ureido, N'-trifluoromethyl,N'-methylureido, N'-trifluoromethyl,N'-ethylureido, N'-

trifluoromethyl,N'-(n-propyl)ureido, N'-trifluoromethyl,N'-(i-propyl)ureido, N'-trifluoromethyl,N'-(n-butyl)ureido, N'-trifluoromethyl,N'-(sec-butyl)ureido, N'-difluoromethyl,N'-methylureido, N'-difluoromethyl,N'-ethylureido, N'-difluoromethyl,N'(n-propyl)ureido, N'-difluoromethyl,N'-(i-propyl)ureido, N'-difluoromethyl,N'-(n-butyl)ureido, N'-difluoromethyl,N'-(sec-butyl)ureido, N'-difluoromethyl,N'-(t-butyl)ureido, N'-difluoromethyl,N'-trifluoromethylureido, N'-hydroxymethyl,N'-methylureido, N'-ethyl,N'-hydroxymethylureido, N'-hydroxymethyl,N'-(n-propyl)ureido, N'-hydroxymethyl,N'-(i-propyl)ureido, N'-n-butyl,N'-hydroxymethylureido, N'-sec-butyl,N'-hydroxymethylureido, N'-t-butyl,N'-hydroxymethylureido, N'-difluoromethyl,N'-hydroxymethylureido, N'-hydroxymethyl,N'-trifluoromethylureido, N'-hydroxyethyl,N'-methylureido, N'-ethyl,N'-hydroxyethylureido, N'-hydroxyethyl,N'-(n-propyl)ureido, N'-hydroxyethyl,N'-(i-propyl)ureido, N'-(n-butyl),N'-hydroxyethylureido, N'(sec-butyl),N'-hydroxyethylureido, N'-(t-butyl),N'-hydroxyethylureido, N'-difluoromethyl,N'-hydroxyethylureido, N'-hydroxyethyl,N'-trifluoromethylureido, N'-hydroxypropyl,N'-methylureido, N'-ethyl,N'-hydroxypropylureido, N'-hydroxypropyl,N'-(n-propyl)ureido, N'-hydroxypropyl,N'-(i-propyl)ureido, N'-(n-butyl),N'-hydroxypropylureido, N'(sec-butyl),N'-hydroxypropylureido, N'(t-butyl),N'-hydroxypropylureido, N'-difluoromethyl,N'-hydroxypropylureido y N'-hydroxypropyl,N'-trifluoromethylureido.

As used herein, the term acyl embraces optionally substituted, linear or branched radicals having 2 to 20 carbon atoms or, preferably 2 to 12 carbon atoms attached to a carbonyl radical. More preferably acyl radicals are "lower acyl" radicals of formula –COR, wherein R is a hydrocarbon group, preferably an alkyl group, having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms.

An acyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an acyl group are themselves unsubstituted.

Preferred optionally substituted acyl radicals include acetyl, propionyl, butiryl, isobutiryl, isovaleryl, pivaloyil, valeryl, lauryl, myristyl, stearyl and palmityl,

As used herein, the term aryl radical embraces typically a C_5-C_{14} monocyclic or polycyclic aryl radical such as phenyl, naphthyl, anthranyl and phenanthryl. Phenyl is preferred.

A said optionally substituted aryl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups, alkoxycarbonyl groups in which the alkyl moiety has from 1 to 4 carbon atoms, hydroxycarbonyl groups, carbamoyl groups, nitro groups, cyano groups, C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups and C_1-C_4 hydroxyalkyl groups. When an aryl radical carries 2 or more substituents, the substituents may be the same or different. Unless otherwise specified, the substituents on an aryl group are typically themselves unsubstituted.

As used herein, the term heteroaryl radical embraces typically a 5- to 14- membered ring system, preferably a 5- to 10- membered ring system, comprising at least one heteroaromatic ring and containing at least one heteroatom selected from O, S and N. A heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

A said optionally substituted heteroaryl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine, chlorine or bromine atoms, alkoxycarbonyl groups in which the alkyl moiety has from 1 to 4 carbon atoms, nitro groups, hydroxy groups, C_1-C_4 alkyl groups and C_1-C_4 alkoxy groups. When an heteroaryl radical carries 2 or more substituents, the substituents may be the same or different. Unless otherwise specified, the substituents on a heteroaryl radical are typically themselves unsubstituted.

Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, benzofuranyl, oxadiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, pyridinyl, benzothiazolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, quinolizinyl, cinnolinyl, triazolyl, indolizinyl, indolinyl, isoindolinyl, isoindolyl, imidazolidinyl, pteridinyl,

thianthrenyl, pyrazolyl, 2H-pyrazolo[3,4-d]pyrimidinyl, 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d] pyrimidnyl and the various pyrrolopyridyl radicals.

The mention of optionally substituted heteroaryl radicals or rests within the present invention is intended to cover the N-oxides obtainable from these radicals when they comprise N-atoms.

Oxadiazolyl, oxazolyl, pyridyl, pyrrolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, furanyl, quinolinyl, isoquinolinyl, indolyl, benzoxazolyl, naphthyridinyl, benzofuranyl, pyrazinyl, pyrimidinyl and the various pyrrolopyridyl radicals are preferred.

As used herein, the term cycloalkyl embraces saturated carbocyclic radicals and, unless otherwise specified, a cycloalkyl radical typically has from 3 to 7 carbon atoms.

A cycloalkyl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. When a cycloalkyl radical carries 2 or more substituents, the substituents may be the same or different. Typically the substituents on a cycloalkyl group are themselves unsubstituted.

Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. It is preferably cyclopropyl, cyclopentyl and cyclohexyl.

As used herein, the term cycloalkenyl embraces partially unsaturated carbocyclic radicals and, unless otherwise specified, a cycloalkenyl radical typically has from 3 to 7 carbon atoms.

A cycloalkenyl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. When a cycloalkenyl radical carries 2 or more substituents, the substituents may be the same or different. Typically, the substituents on a cycloalkenyl group are themselves unsubstituted.

Examples include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. Cyclopentenyl and cyclohexenyl are preferred.

As used herein, the term heterocyclyl radical embraces typically a non-aromatic, saturated or unsaturated C_3-C_{10} carbocyclic ring , such as a 5, 6 or 7 membered radical, in which one or more, for example 1, 2, 3 or 4 of the carbon atoms preferably 1or 2 of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl radicals are preferred. A heterocyclic radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. When a heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

A said optionally substituted heterocyclyl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a heterocyclyl radical are themselves unsubstituted.

Examples of heterocyclic radicals include piperidyl, pyrrolidyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl, cromanyl, isocromanyl, imidazolidinyl, imidazolyl, oxiranyl, azaridinyl, 4,5-dihydro-oxazolyl and 3-aza-tetrahydrofuranyl.

Where a heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, some of the atoms, radicals, moieties, chains and cycles present in the general structures of the invention are "optionally substituted". This means that these atoms, radicals, moieties, chains and cycles can be either unsubstituted or substituted in any poisition by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains and cycles are replaced by chemically acceptable atoms, radicals, moieties, chains and cycles. When two or more substituents are present, each substituent may be the same or different. The substituents are typically themselves unsubstituted.

Typically when a cyclic radical is bridged by an alkylene or alkylenedioxy radical, the bridging alkylene radical is attached to the ring at non-adjacent atoms.

As used herein, the term halogen atom embraces chlorine, fluorine, bromine and iodine atoms. A halogen atom is typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

As used herein, an acylamino group is typically a said acyl group attached to an amino group.

As used herein an alkylenedioxy group is typically -O-R-O-, wherein R is a said alkylene group.

As used herein, an alkoxyacyl group is typically a said alkoxy group attached to a said acyl group.

As used herein, an acyloxy group is typically a said acyl group attached to an oxygen atom.

As used herein, a cycloalkoxy group is typically a said cycloalkyl group attached to an oxygen atom.

Compounds containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers.

As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

According to one embodiment of the present invention in the compounds of formula (I) R^2 represents a hydrogen atom or an aryl group, for example a phenyl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and nitro, C_1-C_4 alkoxy, C_1-C_4 hydroxyalkyl and -CO_2-(C_1-C_4 alkyl) groups. More preferably, R^2 is a hydrogen atom or a phenyl group which is unsubstitued or substituted with 1 or 2 unsubstituted substituents selected from fluorine, chlorine, nitro, C_1-C_4 hydroxyalkyl and -CO_2-(C_1-C_2 alkyl) substituents. Most preferably R^2 is hydrogen.

In another embodiment of the present invention in the compounds of formula (I) R^1 represents a group selected from:

- a (C_{1-4}) alkyl group which is optionally substituted by one or more, for example 1, 2, 3 or 4 hydroxy groups;
- a group of formula

$$-(CH_2)_n-R^6$$

wherein n is an integer from 1 to 3 and R^6 represents a (C_{3-6}) cycloalkyl group.

More preferably, R^1 is an unsubstituted C_1-C_4 alkyl, an unsubstituted C_1-C_4 hydroxyalkyl or an unsubstituted cyclopropyl-(C_1-C_4 alkyl)- group.

In still another embodiment of the present invention in the compounds of formula (I) R^3 represents a group selected from monocyclic or polycyclic aryl or heteroaryl groups, which are optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from:

- halogen atoms;
- (C_1-C_4) alkyl groups, which are optionally substituted by one or more, for example 1, 2, 3 or 4 hydroxy groups;
- and (C_1-C_4) alkoxy, nitro, hydroxy, hydroxycarbonyl, carbamoyl, (C_1-C_4 alkoxy)-carbonyl and cyano groups

In another embodiment of the present invention in the compounds of formula (I), R^3 represents a monocyclic or polycyclic aryl or heteroaryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from:

- halogen atoms;
- alkyl and alkylene groups, which are optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms; and
- phenyl, hydroxy, hydroxycarbonyl, hydroxyalkyl, alkoxycarbonyl, alkoxy, cycloalkoxy, nitro, aryloxy, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphamoyl, acyl, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulphamido, aminosulphonyl, mono- or di-alkylaminosulphonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

More preferably, R^3 represents a phenyl group, a naphthyl group or a 5- to 14-membered monocylic or polycyclic heteroaryl group containing 1, 2 or 3 heteroatoms selected from N, O and S, the phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with 1 or 2 unsubstituted substituents selected from:

- halogen atoms, for example fluorine and chlorine atoms;
- C_1-C_4 alkyl and C_1-C_4 hydroxyalkyl groups; and
- C_1-C_4 alkoxy, nitro, hydroxy, hydroxycarbonyl, carbamoyl, (C_1-C_4 alkoxy)-carbonyl and cyano groups.

Still more preferably R^3 represents a phenyl group, a naphtyl group or a substituted or unsubtituted heteroaryl group selected from substituted or unsubstituted oxadiazolyl, oxazolyl, pyridyl, pyrrolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, furanyl, quinolinyl, isoquinolinyl, indolyl, benzoxazolyl, naphthyridinyl, benzofuranyl, pyrazinyl, pyrimidinyl and the various pyrrolopyridyl radicals.

In another embodiment of the present invention in the compounds of formula (I) R^4 represents

- an unsubstituted mono-(C_1-C_4 alkyl)amino or di-(C_1-C_4 alkyl)amino group;
- a C_1-C_4 alkyl group which is unsubstituted or substituted by one or more, for example 1 or 2, substituents selected from hydroxy, C_1-C_4 alkoxy, amino, mono-(C_1-C_4 alkyl)amino and di-(C_1-C_4 alkyl)amino groups;

- an unsubstituted phenyl-(C_1-C_4 alkyl)- group; or
- a group of formula

$$-(CH_2)_n-R^6$$

wherein n is 2 and R^6 represents a radical selected from phenyl, pyridyl and thienyl optionally substituted by one or more substituents selected from halogen atoms and alkyl, hydroxy, alkoxy, alkylenedioxy, amino, mono- or di-alkylamino, nitro, ciano and trifluoromethyl groups.

More preferably, R^4 represents an alkyl group having from 1 to 6 carbon atoms and which is unsubstituted or substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and hydroxy groups.

In yet another embodiment of the present invention in the compounds of formula (I) R^5 represents a group $COOR^7$ or a monocyclic or polycyclic aryl or heteroaryl group, which is optionally substituted by one or more substituents selected from halogen atoms, C_1-C_4 alkyl groups, C_1-C_4 alkoxycarbonyl groups, a hydroxycarbonyl group and C_1-C_4 alkoxy groups, wherein R^7 is as defined above.

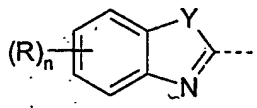
In another preferred embodiment of the present invention in the compounds of formula (I) R^5 represents a group $-COOR^7$ or a monocyclic or polycyclic aryl or heteroaryl group, which is optionally substituted by one or more, for example 1, 2, 3 or 4, substituents selected from halogen atoms and C_1-C_4 alkoxy groups, wherein R^7 has the meaning defined above.

More preferably, R^5 represents $-CO_2R^7$, wherein R^7 represents an unsubstituted C_1-C_4 alkyl group, or R_5 represents a phenyl group or a 5- to 10- membered monocyclic or polycyclic heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, the phenyl and heteroaryl groups being unsubstituted or substituted by 1 or 2 substituents selected from C_1-C_4 alkoxy groups and halogen atoms, for example chlorine and fluorine atoms.

Still more preferably R^5 represents a phenyl group, or a substituted or unsubtituted heteroaryl group selected from substituted or unsubstituted oxadiazolyl, oxazolyl,

pyridyl, pyrrolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, furanyl, quinolinyl, isoquinolinyl, indolyl, benzoxazolyl, naphthyridinyl, benzofuranyl, pyrazinyl, pyrimidinyl and the various pyrrolopyridyl radicals.

Finally in another embodiment of the present invention, when R^5 represents a polycyclic heteroaryl group it is typically a group of formula (XXIII):



(XXIII)

wherein Y represents an O atom, a S atom or a –NH- group, n is 0, 1 or 2 and each R is the same or different and is a halogen atom or a C_1-C_4 alkoxy group.

Particular individual compounds of the invention include:

5-acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[(3,5-dichlorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-(1-naphthylamino)-6-pyridin-3-ylpyridazin-3(2H)-one
methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzoate
5-acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-3-ylpyridazin-3(2H)-one
3-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile
5-acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-2-(cyclopropylmethyl)-4-[(3,5-dichlorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-2-(cyclopropylmethyl)-4-[(2-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[(2-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one
3-{[5-acetyl-2-(cyclopropylmethyl)-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

methyl 4-{[5-acetyl-2-(2-hydroxyethyl)-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl]amino}benzoate

5-acetyl-4-[(2-fluorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

5-acetyl-4-[(2-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

5-acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-2-ylpyridazin-3(2H)-one

3-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-2-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

5-acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-2-ylpyridazin-3(2H)-one

3-{[5-acetyl-2-(cyclopropylmethyl)-3-oxo-6-pyridin-2-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-2-ylpyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-4-[(3,5-dichlorophenyl)amino]-6-pyridin-2-ylpyridazin-3(2H)-one

3-{[5-acetyl-2-(2-hydroxyethyl)-3-oxo-6-pyridin-2-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

5-acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

5-acetyl-4-[(3,5-dichlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

5-acetyl-2-(2-hydroxyethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-2-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(1-naphthylamino)-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzoate

5-acetyl-2-ethyl-4-[(2-methoxyphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

3-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

5-acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-4-ylpyridazin-3(2H)-one

4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzoic acid
5-acetyl-2-(cyclopropylmethyl)-4-[(2-fluorophenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[(2-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one
3-{[5-acetyl-2-(cyclopropylmethyl)-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile
5-acetyl-2-(cyclopropylmethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[(2-fluorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[(2-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one
3-{[5-acetyl-2-(2-hydroxyethyl)-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile
5-acetyl-2-(2-hydroxyethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-thien-2-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[bis-(4-methoxycarbonylphenyl)-amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-{bis[4-(hydroxymethyl)phenyl]amino}-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3-nitrophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3,5-dichlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(4-methoxycarbonylphenyl)amino]-2-(2-hydroxyethyl)-6- pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

5-acetyl-4-[bis(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-4-[(3,5-dichloropyridin-4-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(pyrazin-2-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(pyrimidin-2-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(5-nitropyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(1h-indol-4-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-4-(1,3-benzothiazol-6-ylamino)-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(thianthren-1-ylamino)pyridazin-3(2H)-one

methyl 3-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]thiophene-2-carboxylate

5-acetyl-2-ethyl-4-[(4-methylpyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(1h-1,2,4-triazol-5-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(6-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(2H-indazol-5-ylamino)-6-phenylpyridazin-3(2H)-one

methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]thiophene-3-carboxylate

5-acetyl-2-ethyl-6-phenyl-4-(pyridin-2-ylamino)pyridazin-3(2H)-one

3-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]thiophene-2-carboxylic acid

5-acetyl-2-ethyl-4-[(3-methylcinnolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(2-methylquinolin-8-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(1h-indol-5-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-5-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(6-methoxyquinolin-8-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-4-[(5-bromoquinolin-8-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(4-methylpyrimidin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-fluorophenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-6-(3-fluorophenyl)-2-isopropyl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-6-(3-fluorophenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-6-(1h-benzimidazol-2-yl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one

5-acetyl-6-(1,3-benzoxazol-2-yl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one

5-acetyl-6-(1,3-benzoxazol-2-yl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2H)-one

5-acetyl-6-benzooxazol-2-yl-4-[bis-(3-chlorophenyl)-amino]-2-ethyl-pyridazin-3(2H)-one

5-acetyl-6-benzooxazol-2-yl-4-[bis-(3-fluorophenyl)-amino]-2-ethyl-pyridazin-3(2H)-one

3-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzamide

5-acetyl-2-ethyl-4-(isoquinolin-1-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-4-[(2-butylquinazolin-4-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-4-(1,2-benzisothiazol-3-ylamino)-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(pyridin-4-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(2-hydroxy-7h-purin-6-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(quinazolin-4-ylamino)pyridazin-3(2H)-one

5-acetyl-4-[(4-chloro-1H-indazol-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-4-[(7-chloroquinolin-4-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-4-[(4,6-dichloropyrimidin-2-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(6-hydroxy-2H-pyrazolo[3,4-d]pyrimidin-4-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(2-methylquinolin-4-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(1H-imidazol-2-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(quinolin-4-ylamino)pyridazin-3(2H)-one

5-acetyl-4-(cinnolin-4-ylamino)-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(thieno[2,3-d]pyrimidin-4-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(1H-indazol-6-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(2-methoxypyridin-4-yl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-(6-methoxypyridin-3-yl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-thien-3-ylpyridazin-3(2H)-one

5-acetyl-6-(1-benzofuran-5-yl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2H)-one

1-ethyl-5-[(3-methoxyphenyl)amino]-n,n-dimethyl-6-oxo-3-pyridin-3-yl-1,6-dihydropyridazine-4-carboxamide

5-[(3-chlorophenyl)amino]-1-ethyl-n-methyl-6-oxo-3-pyridin-4-yl-1,6-dihydropyridazine-4-carboxamide

2-ethyl-4-[(3-fluorophenyl)amino]-5-glycoloyl-6-pyridin-4-ylpyridazin-3(2H)-one

2-ethyl-4-[(3-fluorophenyl)amino]-5-(methoxyacetyl)-6-pyridin-3-ylpyridazin-3(2H)-one

5-[(dimethylamino)acetyl]-2-ethyl-4-[(3-methoxyphenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

2-ethyl-4-[(3-fluorophenyl)amino]-5-[(methylamino)acetyl]-6-pyridin-4-ylpyridazin-3(2H)-one

3-{[2-ethyl-3-oxo-5-(3-phenylpropanoyl)-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl]amino}benzamide

ethyl 4-acetyl-5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate

ethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate

5-acetyl-6-(1,3-benzoxazol-2-yl)-2-ethyl-4-[(3-methoxyphenyl)amino]pyridazin-3(2H)-one

5-acetyl-6-(1,3-benzoxazol-2-yl)-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(1,6-naphthyridin-8-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(5-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-pyridin-4-yl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(4-methylpyridin-3-yl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-pyridin-4-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(4-methylpyridin-3-yl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-pyridin-3-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-pyridin-3-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(quinolin-5-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(pyridin-3-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

4-[(5-acetyl-2-ethyl-3-oxo-6-thien-2-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

5-acetyl-2-ethyl-6-thien-2-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

5-Acetyl-4-(bis (4-cyanophenyl)amino)- 2-ethyl-6-thien-2-ylpyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-4-(quinolin-5-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-4-(pyridin-3-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(quinolin-5-ylamino)-6-thien-3-ylpyridazin-3(2H)-one

5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-thien-3-ylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-(pyridin-3-ylamino)-6-thien-3-ylpyridazin-3(2H)-one
4-[(5-acetyl-2-ethyl-3-oxo-6-thien-3-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile
5-acetyl-2-ethyl-6-thien-3-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one
2-ethyl-6-phenyl-5-(3-phenylpropanoyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
2-ethyl-6-phenyl-5-(3-phenylpropanoyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one
2-ethyl-4-(isoquinolin-4-ylamino)-6-phenyl-5-(3-phenylpropanoyl)pyridazin-3(2H)-one
2-ethyl-6-phenyl-4-(quinolin-5-ylamino)-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one
2-ethyl-6-phenyl-4-(pyridin-3-ylamino)-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one
5-acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridazin-3(2H)-one
5-acetyl-6-(1,3-benzothiazol-2-yl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one
5-acetyl-6-(1-benzofuran-2-yl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one
5-acetyl-2-ethyl-6-pyridin-3-yl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one
4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzoic acid
5-acetyl-2-ethyl-4-[(1-oxidopyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one
ethyl 3-(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-ylamino)benzoate
3-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzamide
5-acetyl-2-ethyl-6-phenyl-4-(thieno[2,3-b]pyridin-3-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(6-fluoropyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(2-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-4-{[2-(dimethylamino)pyridin-3-yl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one
5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]pyridine-2-carboxylic acid
5-acetyl-2-ethyl-4-[(2-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-(1H-indazol-4-ylamino)-6-phenylpyridazin-3(2H)-one
5-acetyl-4-[(2-chloropyridin-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-acetyl-4-[(5-chloropyridin-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]nicotinamide
5-acetyl-2-ethyl-4-(1,7-naphthyridin-8-ylamino)-6-phenylpyridazin-3(2H)-one
2-ethyl-5-glycoloyl-4-[(2-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one
methyl 5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]nicotinate
5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]nicotinic acid
5-acetyl-2-ethyl-4-(1,5-naphthyridin-3-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(8-hydroxy-1,7-naphthyridin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(thien-2-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-[(2-phenylpyridin-3-yl)amino]pyridazin-3(2H)-one

ethyl {5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]pyridin-2-yl}acetate

5-acetyl-2-ethyl-4-[(6-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(6-hydroxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(2-fluoropyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-4-[(6-chloro-4-methylpyridin-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(3-hydroxypyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-[(4-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-8-ylamino)-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-6-phenyl-4-(quinolin-7-ylamino)pyridazin-3(2H)-one

5-acetyl-4-[(5-chloropyridin-3-yl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-methoxypyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-4-[(2-chloropyridin-3-yl)amino]-2-ethyl-6-(4-fluorophenyl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-fluoropyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-4-[(2-chloropyridin-3-yl)amino]-2-(cyclopropylmethyl)-6-(4-fluorophenyl)pyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(2-methoxypyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(2-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(2-fluoropyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(pyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(2-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-6-(3-chlorophenyl)-4-[(2-chloropyridin-3-yl)amino]-2-ethylpyridazin-3(2H)-one

5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

methyl 5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]quinoline-8-carboxylate

5-acetyl-2-ethyl-4-[(4-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(4-methoxyphenyl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methoxyphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methoxyphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methoxy-phenyl)-4-(1-oxy-quinolin-5-ylamino)-2H-pyridazin-3-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(3-methoxyphenyl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-methoxyphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-methoxyphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-methoxyphenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(4-methylphenyl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methylphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methylphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methylphenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(4-methylphenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

5-acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(3-methylphenyl)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-methylphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-methylphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

5-acetyl-2-ethyl-6-(3-methylphenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

methyl 4-[4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl]benzoate

methyl 4-[4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoate

4-[4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoic acid

methyl 4-{4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazin-3-yl}benzoate

4-{4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazin-3-yl}benzoic acid

methyl 3-[4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoate

3-[4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoic acid

5-acetyl-4-[(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-4-[bis(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

5-acetyl-4-[(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
5-acetyl-4-[bis(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one
methyl [4-acetyl-6-oxo-3-phenyl-5-(quinolin-5-ylamino)pyridazin-1(6H)-yl]acetate
[4-acetyl-6-oxo-3-phenyl-5-(quinolin-5-ylamino)pyridazin-1(6H)-yl]acetic acid
5-acetyl-2-ethyl-4-[(3-methylpyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-6-phenyl-4-(1H-pyrazol-3-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-phenyl-4-(9H-purin-6-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(3-methylisoxazol-5-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(8-hydroxyquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-(1H-indazol-7-ylamino)-6-phenylpyridazin-3(2H)-one
5-acetyl-4-[(6-bromoquinolin-8-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(5-methylisoxazol-3-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-(isoxazol-3-ylamino)-6-phenylpyridazin-3(2H)-one
5-acetyl-2-(cyclopropylmethyl)-6-phenyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-2-(cyclopropylmethyl)-6-phenyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(1-methyl-1H-pyrazol-3-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(1-oxidoquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(2-oxidoisoquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-pyridin-4-yl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-pyridin-3-yl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(8-fluoroquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-(quinolin-8-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-(quinolin-8-ylamino)pyridazin-3(2H)-one
5-acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one
5-acetyl-2-ethyl-4-[(2-methylquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one
5-acetyl-6-(3-chlorophenyl)-2-ethyl-4-(isoquinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-(3-fluorophenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one
5-acetyl-2-ethyl-6-(3-fluorophenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]quinoline-8-carboxylic acid

and pharmaceutically acceptable salts thereof.

Of outstanding interest are:

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-pyridin-3-ylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-pyridin-4-ylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

4-[(5-Acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-thien-2-ylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-phenyl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-phenyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(1H-indol-4-ylamino)-6-phenylpyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-phenyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

5-Acetyl-6-(3-fluorophenyl)-2-isopropyl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-Acetyl-2-(cyclopropylmethyl)-6-(3-fluorophenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

5-Acetyl-2-ethyl-4-(isoquinolin-5-ylamino)-6-phenylpyridazin-3(2H)-one

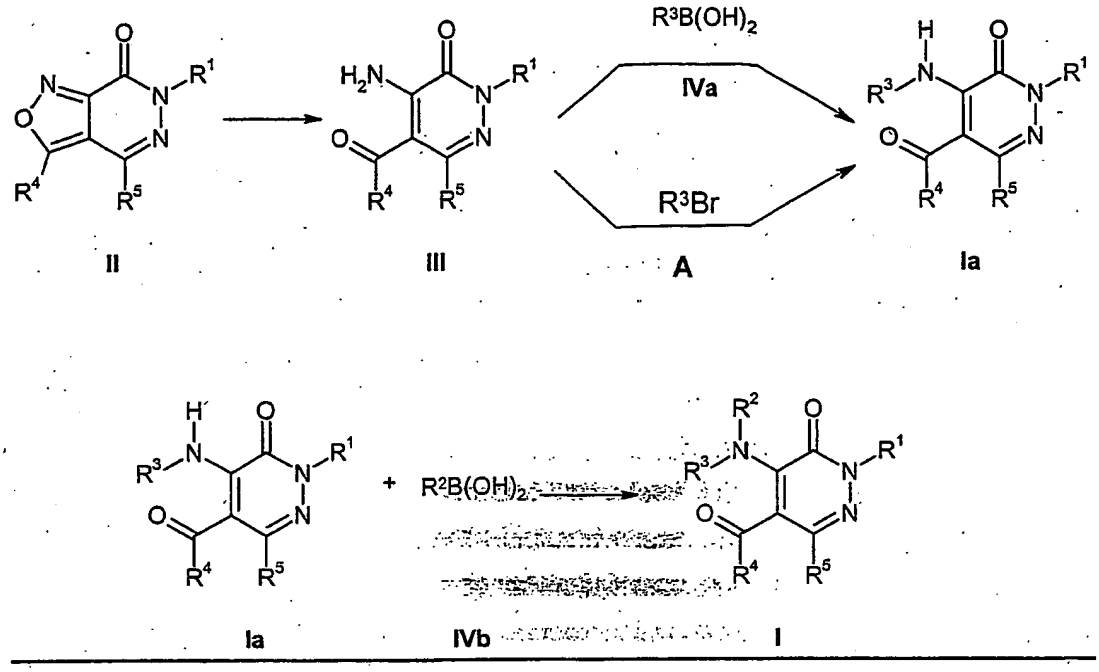
5-Acetyl-6-(1,3-benzoxazol-2-yl)-2-ethyl-4-[(3-fluorophenyl)amino]pyridazin-3(2H)-one

and pharmaceutically acceptable salts thereof.

The compounds of the present invention may be prepared by one of the processes described below.

Compounds (I) may be obtained as shown in Scheme 1.

Scheme 1



An isoxazolo[3,4-d]pyridazin-7(6H)-one of formula (II), wherein R^1, R^4 and R^5 are as hereinbefore defined, is hydrogenated to yield an 4-aminopyridazin-3(2*H*)-one derivative (III), wherein R^1, R^4 and R^5 are as hereinbefore defined. The hydrogenation may be performed using for example hydrogen in the presence of a catalyst by methods known per se, e. g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173. Alternatively, the reaction may be accomplished by transfer hydrogenation using an organic hydrogen donor and a transfer agent, such as ammonium formate or hydrazine by methods known per se, e. g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173.

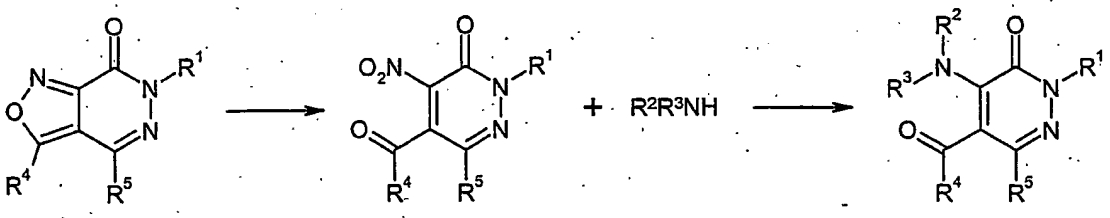
Condensation of 4-aminopyridazin-3(2*H*)-ones (III) with an aryl or heteroaryl bromide of formula (A) wherein R^3 is as hereinbefore defined, gives compounds (Ia), wherein R^1, R^3, R^4 and R^5 are as hereinbefore defined. The reaction is carried out in the presence of a copper salt such as cuprous iodide and an inorganic base such as potassium phosphate, potassium carbonate or sodium carbonate and can also be performed in the presence of an organic base, preferably a diamine base such as N, N'-dimethylethylenediamine in an inert solvent such as toluene, dioxane or dimethylformamide, at a temperature from -20°C to the boiling point of the solvent. It can also be performed neat.

Alternatively, condensation of 4-aminopyridazin-3(2*H*)-one derivative (III), wherein R^1, R^4 and R^5 are as hereinbefore defined, with a boronic acid of formula (IVa), wherein R^3 is as hereinbefore defined, gives compound (Ia), wherein R^1, R^3, R^4 and R^5 are as hereinbefore defined. The reaction is carried out in the presence of a copper salt such as cupric acetate and an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from - 20° C to the boiling point of the solvent. Compounds (Ia) are equal to compounds (I) when R^2 is hydrogen.

Condensation of an 4-aminopyridazin-3(2*H*)-one derivative (Ia), wherein R^1, R^3, R^4 and R^5 are as hereinbefore defined, with a boronic acid (IVb), wherein R^2 is as hereinbefore defined, gives compounds (I), wherein R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined. The reaction is carried out in the presence of a copper salt such as cupric acetate in the presence of an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from - 20° C to the boiling point of the solvent.

Alternatively, compounds (I) may be obtained as shown in Scheme 2.

Scheme 2

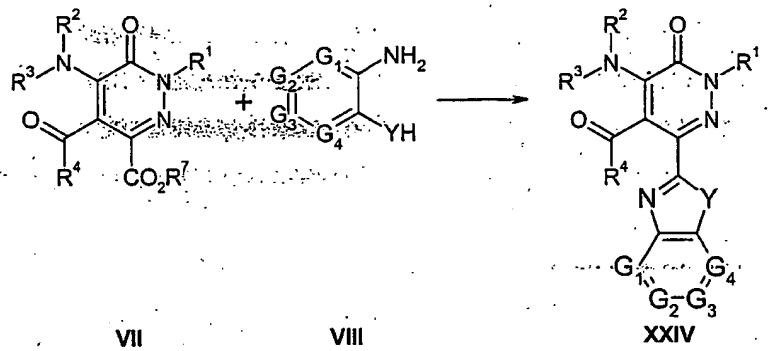


Oxidation of an isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one of formula (II), wherein R^1, R^4 and R^5 are as hereinbefore defined, gives a 4-nitropyridazin-3(2*H*)-one derivative of formula (V), wherein R^1, R^4 and R^5 are as hereinbefore defined. The reaction may be performed using an oxidising agent such as cerium ammonium nitrate under acidic conditions by methods known per se, e. g. V. Dal Piaz et al. *Synthesis*, **1989**, 213.

Condensation of the 4-nitropyridazin-3(2*H*)-one derivative of formula (V), wherein R^1, R^4 and R^5 are as hereinbefore defined, with the corresponding amine (VI), wherein R^2 and R^3 are as hereinbefore defined, following methods known per se, e. g. G. Ciciani et al. *Farmaco* **1991**, *46*, 873, gives compound (I), wherein R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined.

According to one aspect of the present invention some specific compounds of formula (I) and in particular those of formula (XXIV) may also be obtained as shown in Scheme 3.

Scheme 3

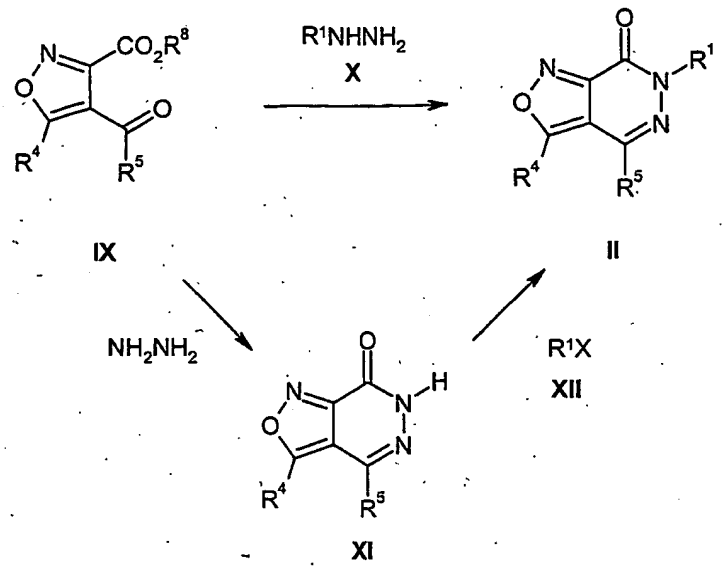


VII VIII XXIV

Condensation of compounds (VII), in which R^7 is an alkyl group, with an ortho-substituted aryl or heteroarylamine of formula (VIII), wherein each G_1, G_2, G_3 and G_4 independently represent a nitrogen or carbon atom and -YH represents an amino, a mercapto or a hydroxy substituent, in the presence of a dehydrating agent such as trimethylaluminium, gives pyridazin-3(2H)-ones of formula (I) wherein R^1, R^4 and R^5 are as hereinbefore defined and Y represents a sulphur atom, an oxygen atom or a –NH- group. The reaction is preferably carried out in a solvent such as toluene at a temperature between -78 degrees and room temperature.

Isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (II) may be obtained as shown in Scheme 4.

Scheme 4

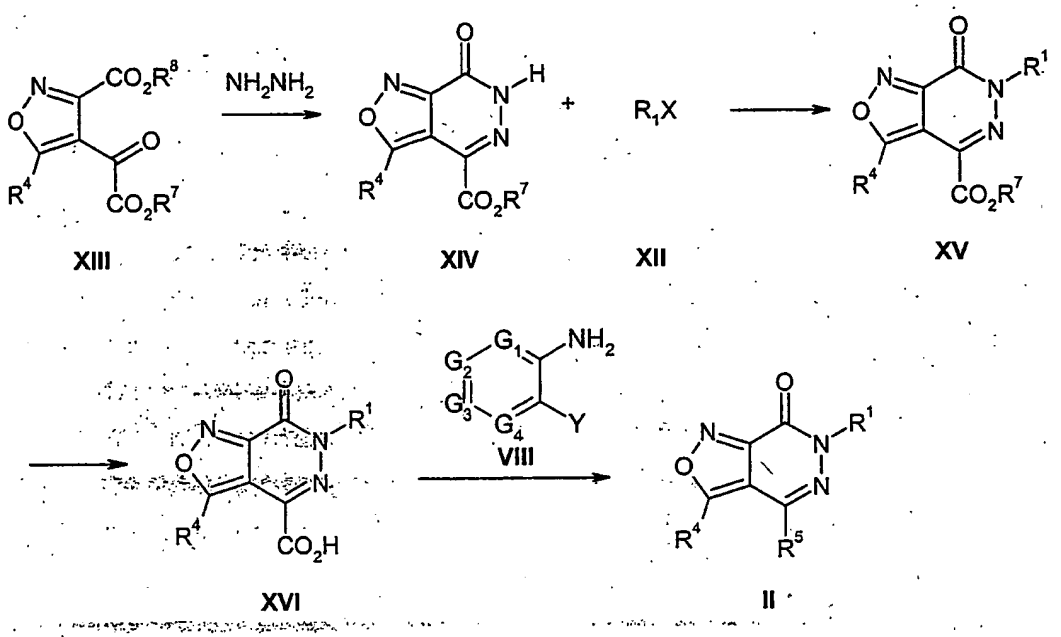


Isoxazole derivatives of formula (IX), where R^4 and R^5 are as hereinbefore defined and R^8 is an alkyl group, are condensed with a hydrazine of formula (X), where R^1 is as hereinbefore defined, by methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478, to give isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (II) wherein R^1, R^4 and R^5 are as hereinbefore defined.

Alternatively, isoxazole derivatives of formula (IX), where R^4 and R^5 are as hereinbefore defined and R^8 is an alkyl group, are condensed with hydrazine, by methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478, to give isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (XI) wherein R^4 and R^5 are as hereinbefore defined. Subsequent reaction with an alkylating agent of formula (XII), wherein R^1 is as hereinbefore defined and X is a leaving group such as a chlorine or a bromine atom or a methanesulfonate, p-toluenesulfonate or a benzenesulfonate group by methods known per se, e. g. V. Dal Piaz et al. *Drug Des. Discovery* **1996**, *14*, 53; or condensation with an alcohol of formula (XII) wherein R^1 is as hereinbefore described and X is a hydroxy group in the presence of triphenylphosphine and diethylazodicarboxylate by methods known per se, e. G. O. Mitsunobu et al. *J. Am. Chem. Soc.* **1972**, *94*, 679; gives isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (II) wherein R^1, R^4 and R^5 are as hereinbefore defined.

Isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (II) may also be obtained as shown in Scheme 5.

Scheme 5

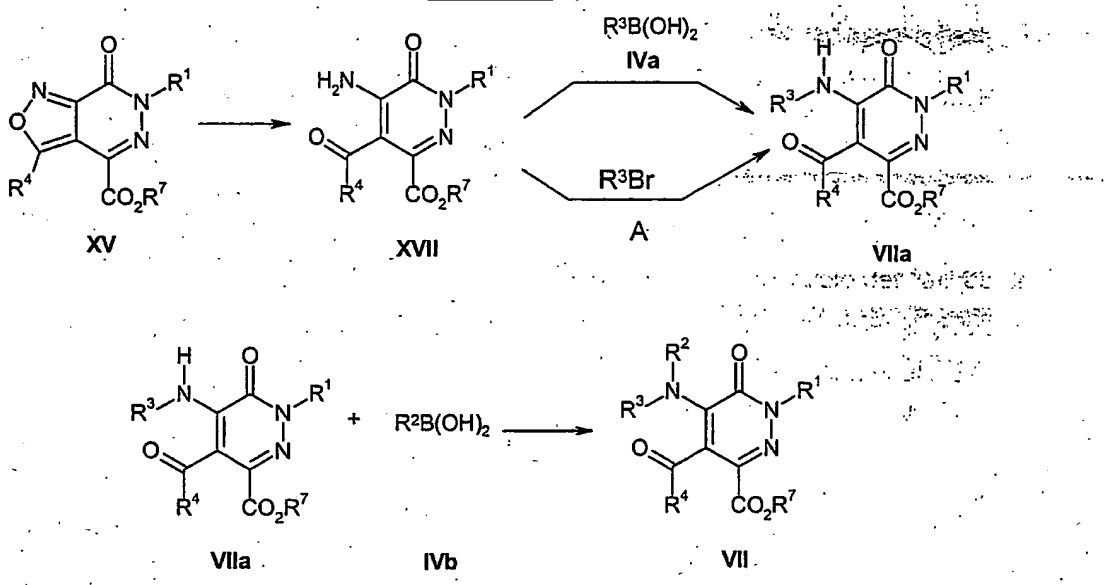


Isoxazole derivatives of formula (XIII), wherein R^4 is hereinbefore defined and R^7 and R^8 are an alkyl group, are condensed with hydrazine, by methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478, to give isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (XIV) wherein R^4 is as hereinbefore defined and R^7 is an alkyl group. Subsequent reaction with an alkylating agent of formula (XII), wherein R^1 is as hereinbefore defined and X is a leaving group such as a chlorine or a bromine atom or a methanesulfonate, p-toluenesulfonate or a benzenesulfonate group, by methods known per se, e. g. V. Dal Piaz et al. *Drug Des. Discovery* **1996**, *14*, 53; or condensation with an alcohol of formula (XII) wherein R^1 is as hereinbefore described and X is a hydroxy group in the presence of triphenylphosphine and diethylazodicarboxylate by methods known per se, e. g. O. Mitsunobu et al. *J. Am. Chem. Soc.* **1972**, *94*, 679; gives isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (XV), wherein R^1 and R^4 are as hereinbefore defined and R^7 is an alkyl group. Compounds (XV) are treated with sodium or potassium hydroxide and further neutralisation with an inorganic acid such as hydrochloric or sulfuric acid provides the corresponding carboxylic acid derivative of formula (XVI), wherein R^1 and R^4 are as hereinbefore

defined. The reaction is preferably carried out in a solvent such as methanol, ethanol, tetrahydrofuran or an aqueous mixture of one of the above mentioned solvents at its boiling point. Condensation of compounds (XVI) with an ortho-substituted aryl or heteroarylamine of formula (VIII), wherein each G_1, G_2, G_3 and G_4 independently represent a nitrogen or carbon atom and Y represents an amino, a mercapto or a hydroxy substituent, in the presence of a dehydrating agent such as polyphosphoric acid or trimethylsilylpolyphosphate gives isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (II) wherein R^1, R^4 and R^5 are as hereinbefore defined. The reaction is preferably carried out in a highly boiling point solvent such as 1,2-dichlorobenzene at its boiling point.

Pyridazin-3(2H)-ones of formula (VII) may be obtained as shown in Scheme 6

Scheme 6

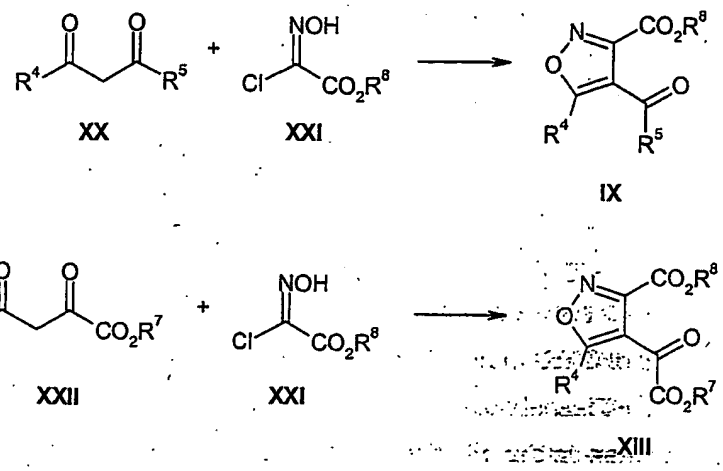


An isoxazolo[3,4-d]pyridazin-7(6H)-one of formula (XV), wherein $R^1$and R^4 are as hereinbefore defined and R^7 is an alkyl group, is hydrogenated to yield an 4-aminopyridazin-3(2*H*)-one derivative (XVII), wherein R^1 and R^4 are as hereinbefore defined and R^7 is an alkyl group. The hydrogenation may be performed using for example hydrogen in the presence of a catalyst by methods known per se, e. g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173. Alternatively, the reaction may be accomplished by transfer hydrogenation using an organic hydrogen donor and a transfer agent, such as ammonium formate or hydrazine by methods known per se, e.

g. V. Dal Piaz et al. *Heterocycles*, **1991**, *32*, 1173. Condensation of an 4-aminopyridazin-3(2*H*)-one derivative (XVII), wherein R^1, R^3 and R^4 are as hereinbefore defined and R^7 is an alkyl group with an aryl or heteroaryl bromide of formula (A) wherein R^3 is as hereinbefore defined, gives compounds (VIIa), wherein R^1, R^3, R^4 and R^5 are as hereinbefore defined. The reaction is carried out in the presence of a copper salt such as cuprous iodide and an inorganic base such as potassium phosphate, potassium carbonate or sodium carbonate and can also be performed in the presence of an organic base, preferably a diamine base such as N, N'-dimethylethylenediamine in an inert solvent such as toluene, dioxane or dimethylformamide, at a temperature from -20°C to the boiling point of the solvent or without solvent. Alternatively, condensation of an 4-aminopyridazin-3(2*H*)-one derivative (XVII), wherein R^1, R^3 and R^4 are as hereinbefore defined and R^7 is an alkyl group, with a boronic acid (IVa), wherein R^3 is as hereinbefore defined, gives compounds (VIIa), wherein R^1, R^3 and R^4 are as hereinbefore defined and R^7 is an alkyl group. The reaction is carried out in the presence of a copper salt such as cupric acetate in the presence of an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from -20°C to the boiling point of the solvent. Compounds (VIIa) are equal to compounds (VII) when R^2 is hydrogen. Condensation of an 4-aminopyridazin-3(2*H*)-one derivative (VIIa), wherein R^1, R^3 and R^4 are as hereinbefore defined and R^7 is an alkyl group, with a boronic acid (IVb), wherein R^2 is as hereinbefore defined, gives compounds (VII), wherein R^1, R^2, R^3 and R^4 are as hereinbefore defined and R^7 is an alkyl group. The reaction is carried out in the presence of a copper salt such as cupric acetate in the presence of an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from -20°C to the boiling point of the solvent.

Isoxazole derivatives of formula (IX) and (XIII) may be obtained as shown in Scheme 7.

Scheme 7

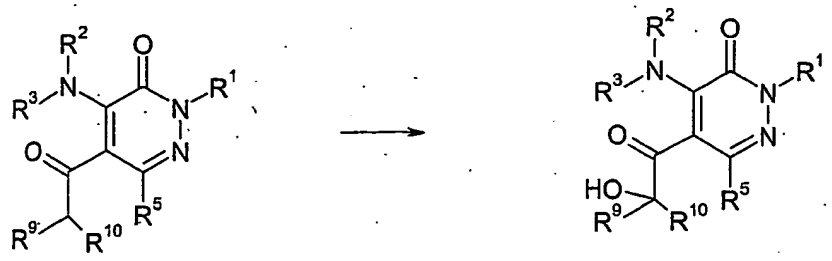


Reaction of a 1,3-dicarbonylic compound of general formula (XX), wherein R^4 and R^5 are as hereinbefore defined, and a 2-chloro-2-(hydroxyimino)acetate derivative of formula (XXI), wherein R^8 is as hereinbefore defined, following methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478, gives isoxazole derivatives of formula (IX), wherein R^4 and R^5 are as hereinbefore defined and R^8 is an alkyl group.

Reaction of a 2,4-dioxoester derivative of general formula (XXII), wherein R^4 is as hereinbefore defined and R^7 is an alkyl group, and a 2-chloro-2-(hydroxyimino)acetate derivative of formula (XXI), wherein R^8 is as hereinbefore defined, following methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, *95*, 1478, gives isoxazole derivatives of formula (XIII), wherein R^4 is as hereinbefore defined and R^7 and R^8 are an alkyl group.

Scheme 8

According to one aspect of the present invention some specific compounds of formula (I) and in particular those of formula (Ic) may also be obtained as shown in Scheme 8.

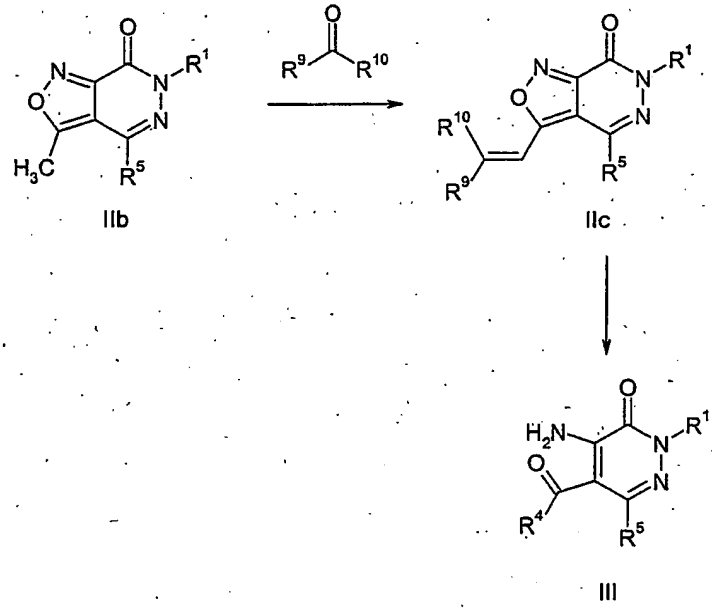


Ib Ic

Reaction of a pyridizinone of formula (Ib) wherein R^1, R^2, R^3 and R^5 are as hereinbefore defined and R^4 is the rest $-CHR^9R^{10}$ wherein are R^9 and R^{10}alkyl or aryl groups with an hypervalent iodine compound by methods known per se (Moriarty, R.M; Hu, H; Gupta S.C., Tetrahedron Lett, 1981, 22, 1283-86) gives the α-hydroxylated derivative (Ic) wherein R^1,R^2,R^3 and R^5 are as hereinbefore defined.

Scheme 9

4-Aminopyridazin-3(2H)-ones of formula (III) may also be obtained as shown in Scheme 9.



IIb IIc III

Condensation of an isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one of formula (IIb) wherein R^1 and R^5 are as defined above with an aldehyde or a ketone of formula R^9COR^{10}, by methods known per se, eg. G. Ciciani et al. *Il Farmaco* **1991**, 46, 873 leads to a substituted vinyl

derivative of formula (IIc) which is then reduced using for example hydrogen in the presence of a catalyst such as palladium on charcoal in a solvent such as methanol, ethanol or ethyl acetate to yield the corresponding 4-aminopyridazin-3(2*H*)-one (III).

When the defined groups R^1 to R^5 are susceptible to chemical reaction under the conditions of the hereinbefore described processes or are incompatible with said processes, conventional protecting groups may be used in accordance with standard practice, for example see T. W. Greene and P. G. M. Wuts in 'Protective Groups in Organic Chemistry', 3rd Edition, John Wiley & Sons (1999). It may be that deprotection will form the last step in the synthesis of compounds of formula (I).

In still another aspect the present invention encompasses intermediate compounds of formula (XVII), (VIIa) and (VII) useful in the synthesis of compounds of formula (I).

The compounds of formulae (IVa), (IVb), (VI), (X), (XII), (VIII), (XX), and (XXII) are known compounds or can be prepared by analogy with known methods.

PHARMACOLOGICAL ACTIVITY

PDE4 Assay Procedure

Compounds to be tested were resuspended in DMSO at a stock concentration of 1 mM. The compounds were tested at different concentrations varying from 10 µM to 10 pM to calculate an IC_{50}. These dilutions were done in 96-well plates. In some cases, plates containing diluted compounds were frozen before being assayed. In these cases, the plates were thawed at room temperature and stirred for 15 minutes.

Ten microliters of the diluted compounds were poured into a "low binding" assay plate. Eighty microliters of reaction mixture containing 50 mM Tris pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EGTA, and 15 nM [3H]-cAMP were added to each well. The reaction was initiated by adding ten microliters of a solution containing PDE4. The plate was then incubated under stirring for 1 hour at room temperature. After incubation the reaction was stopped with 50 microlitres of SPA beads, and the reaction was allowed to incubate for another 20 minutes at room temperature before measuring radioactivity using standard instrumentation.

The reaction mixture was prepared by adding 90 ml of H_2O to 10 ml of 10X assay buffer (500 mM Tris pH 7.5, 83 mM $MgCl_2$, 17 mM EGTA), and 40 microlitres 1 μCi/μL [3H]-cAMP. SPA beads solution was prepared by adding 500 mg to 28 ml H_2O for a final concentration of 20 mg/ml beads and 18 mM zinc sulphate.

The results are shown in Table 1.

Example	IC_{50} PDE4 (nM)
1	2.3
4	6.8
31	4.5
32	0.59
33	0.11
36	6.4
41	16
51	29
52	5.2
63	24
67	10
69	2
82	0.3
84	2.6
91	9.4
92	11
93	8.3
96	5.1

It can be seen from Table 1 that the compounds of formula (I) are potent inhibitors of phosphodiesterase 4 (PDE 4). Preferred pyridazin-3(2*H*)-one derivatives of the invention possess an IC_{50} value for the inhibition of PDE4 (determined as defined above) of less than 100 nM, preferably less than 50 nM and most preferably less than

30 nM. The compounds are also capable of blocking the production of some pro-inflammatory cytokines such as, for example, TNFα.

Thus, they can be used in the treatment of allergic, inflammatory and immunological diseases, as well as those diseases or conditions where the blockade of pro-inflammatory cytokines or the selective inhibition of PDE 4 could be of benefit. These disease states include asthma, chronic obstructive pulmonary disease, allergic rhinitis, rheumatoid arthritis, osteoarthritis, osteoporosis, bone-formation disorders, glomerulonephritis, multiple sclerosis, ankylosing spondylitis, Graves ophtalmopathy, myasthenia gravis, diabetes insipidus, graft rejection, gastrointestinal disorders such as irritable bowel disease, ulcerative colitis or Crohn disease, septic shock, adult distress respiratory syndrome, and skin diseases such as atopic dermatitis, contact dermatitis, acute dermatomyositis and psoriasis. They can also be used as improvers of cerebrovascular function as well as in the treatment of other CNS related diseases such as dementia, Alzheimer's disease, depression, and as nootropic agents.

The compounds of the present invention are also of benefit when administered in combination with other drugs such as steroids and immunosuppressive agents, such as cyclosporin A, rapamycin or T-cell receptor blockers. In this case the administration of the compounds allows a reduction of the dosage of the other drugs, thus preventing the appearance of the undesired side effects associated with both steroids and immunosuppressants.

Like other PDE4 inhibitors (see references above) the compounds of the invention can also be used for blocking, after preventive and/or curative treatment, the erosive and ulcerogenic effects induced by a variety of etiological agents, such as antiinflammatory drugs (steroidal or non-steroidal antiinflammatory agents), stress, ammonia, ethanol and concentrated acids.

They can be used alone or in combination with antacids and/or antisecretory drugs in the preventive and/or curative treatment of gastrointestinal pathologies like drug-induced ulcers, peptic ulcers, H. Pylori-related ulcers, esophagitis and gastro-esophageal reflux disease.

They can also be used in the treatment of pathological situations where damage to the cells or tissues is produced through conditions like anoxia or the production of an excess of free radicals. Examples of such beneficial effects are the protection of cardiac tissue after coronary artery occlusion or the prolongation of cell and tissue viability when the compounds of the invention are added to preserving solutions intended for storage of transplant organs or fluids such as blood or sperm. They are also of benefit on tissue repair and wound healing.

Accordingly, the pyridazin-3(2*H*)-one derivatives of the invention and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compound and/or salts thereof, may be used in a method of treatment of disorders of the human body which comprises administering to a patient requiring such treatment an effective amount of a pyridazin-3(2*H*)-one derivative of the invention or a pharmaceutically acceptable salt thereof.

The results of table I show that the compounds of formula (I) are potent inhibitors of phosphodiesterase 4 (PDE4) and are therefore useful in the treatment or prevention of pathological conditions, diseases and disorders known to be susceptible of amelioration by inhibition of PDE4, such as asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

The compounds of the present invention can also be used in combination with other drugs known to be effective in the treatment of these diseases. For example, in combination with steroids, immunosuppressive agents, T-cell receptor blockers and/or antiinflammatory drugs for simultaneous, separate or sequential use in the treatment of the human or animal body

Accordingly, another embodiment of he invention is the use of the compounds of formula (I) in the manufacture of a medicament for treatment or prevention of pathological conditions, diseases and disorders known to be susceptible of amelioration by inhibition of PDE4, as well as a method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by inhibition of PDE4, which comprises administering to said subject an effective amount of a compound of formula (I).

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a pyridazin-3(2*H*)-one derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with at least one pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight, of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such compound, to form the compositions of this invention are well-known per se and the actual excipients used depend inter alia on the intended method of administering the compositions.

Compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid..

Compositions for topical administration may take the form of ointments, creams or lotions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

Effective doses are normally in the range of 10-600 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as a limiting.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples (including Preparation Examples (Preparations 1 to 99)) which do not limit the scope of the invention in any way.

^{1}H Nuclear Magnetic Resonance Spectra were recorded on a Varian Gemini 300 spectrometer.

Low Resolution Mass Spectra (m/z) were recorded on a Micromass ZMD mass spectrometer using ESI ionization.

Melting points were recorded using a Perkin Elmer DSC-7 apparatus.

The chromatographic separations were obtained using a Waters 2695 or 2795 system equipped with a Symmetry C18 (2.1 x 10 mm, 3.5 mM) column using one of the following methods:

Method A). The mobile phase was formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) (B) and formic acid (0.46 mL), ammonia (0.115 mL) and water (1000 mL) (A): initially from 0% to 95% of B in 10.5 min at a flow rate of 0.4 ml/min, from 10.5 to 11.0 min the flow rate was lineary increased to 0.8

ml/min and maintained in these conditions until minute 12.0. Reequilibration time betwen two injections was 2 min. The injection volume was 5 microliter. Diode array chromatograms were collected at 210 nM.

Method B) The mobile phase was formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) (B) and formic acid (0.46 mL), ammonia (0.115 mL) and water (1000 mL) (A): initially from 0% to 95% of B in 20 min, and then 4 min. with 95% of B. The reequilibration time between two injections was 5 min. The flow rate was 0.4 mL/min. The injection volume was 5 microliter. Diode array chromatograms were collected at 210 nM.

PREPARATION EXAMPLES

PREPARATION 1 (Scheme 7)

Ethyl 5-methyl-4-(pyridin-3-ylcarbonyl)isoxazole-3-carboxylate

To an ice-cooled solution of sodium ethoxide (5.9 g, 110 mmol) in absolute ethanol (150 mL) 1-pyridin-3-yl-butane-1,3-dione (Ohta, S. *et al., Chem. Pharm. Bull.*, **1981**, *29*, 2762) (16.4 g, 100 mmol) was added portionwise and the mixture was stirred at 0º for 30 min. A solution of ethyl chloro(hydroximino)acetate (16.7 g, 110 mmol) in absolute ethanol (50 mL) was added dropwise and the final mixture was stirred at room temperature overnight. The mixture was concentrated and the residue thus obtained was suspended in ethyl acetate, washed with saturated NH_4Cl solution, water and brine, dried and concentrated to yield the title compound (25.7 g, 98% yield) as a yellow solid.

δ($CDCl_3$): 1.15 (t, 3H), 2.58 (s, 3H), 4.18 (q, 2H), 7.42 (m, 1H), 8.10 (m, 1H), 8.81 (m, 1H), 8.95 (m, 1H).

PREPARATION 2 (Scheme 7)

Ethyl 5-methyl-4-(pyridin-2-ylcarbonyl)isoxazole-3-carboxylate

Obtained as a yellow solid (99%) from 1-pyridin-2-yl-butane-1,3-dione (Chiswell *et al.*, *Inorg. Chim. Acta* 1972, *6*, 629) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.

LRMS: m/Z 261 $(M+1)^+$.

PREPARATION 3 (Scheme 4)

3-Methyl-4-pyridin-3-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Hydrazine monohydrate (6.0g, 120 mmol) was added dropwise to a solution of the title compound of Preparation 1 (26.0 g, 100 mmol) in dry ethanol (500 mL) and the resulting mixture was stirred overnight. After cooling with an ice bath, a precipitate was formed which was collected by filtration and washed with diethyl ether to yield the title compound (17.2 g, 76% yield) as a yellow solid.

δ(DMSO-d6): 2.57 (s, 3H), 7.58 (m, 1H), 8.10 (m, 1H), 8.72 (d, 1H), 8.80 (s,1H).

PREPARATION 4 (Scheme 4)

3-Methyl-4-pyridin-2-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained as a yellow solid (60%) from the title compound of Preparation 2 using the experimental procedure described in Preparation 3.

δ(DMSO-d6): 2.92 (s, 3H), 7.58 (m, 1H), 7.98 (m, 2H), 8.77 (m, 1H).

PREPARATION 5 (Scheme 4)

6-Ethyl-3-methyl-4-pyridin-3-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

To a suspension of the title compound of Preparation 3 (17.2 g, 75.6 mmol) and anhydrous potassium carbonate (62 g, 453 mmol) in dry dimethylformamide (100 mL) was added ethyl bromide (57.0 g, 525 mmol) and the resulting mixture stirred at r.t. overnight. The mixture was concentrated and the residue thus obtained was suspended in dichloromethane, washed with water and brine, dried and concentrated to yield the title compound (8.44 g, 44% yield) as a yellow solid.

δ($CDCl_3$): 1.42 (t, 3H), 2.58 (s, 3H), 4.23 (q, 2H), 7.55 (m,1H), 7.92 (m,1H), 8.80 (m, 2H).

PREPARATION 6 (Scheme 4)

6-Ethyl-3-methyl-4-pyridin-2-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (27%) from the title compound from Preparation 4 following the experimental procedure described in Preparation 5.

δ($CDCl_3$): 1.41 (t, 3H), 2.98 (s, 3H), 4.33 (q, 2H), 7.42 (m,1H), 7.92 (m,1H), 8.05 (m, 1H), 8.68 (m, 1H).

PREPARATION 7 (Scheme 4)

6-Ethyl-3-methyl-4-pyridin-4-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (82%) from 3-methyl-4-pyridin-4-yl-6H-isoxazolo[3,4-d]pyridazin-7-one (V. Dal Piaz *et al., J. Pharmac. Sci.,* 1991, 80, 341-348) following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.39 (t, 3H), 2.58 (s, 3H), 4.31 (q, 2H), 7.52 (d, 2H), 8.80 (d, 2H).

PREPARATION 8 (Scheme 4)

6-(Cyclopropylmethyl)-3-methyl-4-pyridin-3-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (44%) from the title compound from Preparation 3 and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5.

$\delta(DMSO\text{-}d_6)$: 0.40 (m, 4H), 1.32 (m, 1H), 2.58 (s, 3H), 4.00 (d, 2H), 7.60 (m,1H), 8.10 (m,1H), 8.78 (m, 1H), 8.11 (m, 1H).

PREPARATION 9 (Scheme 4)

6-(Cyclopropylmethyl)-3-methyl-4-pyridin-2-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (98%) from the title compound from Preparation 4 and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 0.55 (m, 4H), 1.42 (m, 1H), 2.98 (s, 3H), 4.03 (d, 2H), 7.40 (m, 1H), 7.82 (m,1H), 8.01 (m, 1H), 8.72 (m, 1H).

PREPARATION 10 (Scheme 4)

6-(Cyclopropylmethyl)-3-methyl-4-pyridin-4-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (85%) from 3-methyl-4-pyridin-4-yl-6H-isoxazolo[3,4-d]pyridazin-7-one (V. Dal Piaz *et al., J. Pharmac. Sci.,* 1991, 80, 341-348) and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5.

δ(DMSO-d_6): 0.54 (m, 4H), 1.35 (m, 1H), 2.58 (s, 3H), 4.01 (d, 2H), 7.65 (d, 2H), 8.78 (d, 2H).

PREPARATION 11 (Scheme 4)

6-(2-Hydroxyethyl)-3-methyl-4-pyridin-3-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (66%) from the title compound from Preparation 3 and 2-bromoethanol following the experimental procedure described in Preparation 5.

δ(DMSO-d_6): 2.60 (s, 3H), 4.05 (m, 2H), 4.41 (t, 3H), 7.52 (m,1H), 7.95 (m, 1H), 8.10 (m,1H), 8.60 (m, 2H).

PREPARATION 12 (Scheme 4)

6-(2-Hydroxyethyl)-3-methyl-4-pyridin-2-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (92%) from the title compound from Preparation 4 and 2-bromoethanol following the experimental procedure described in Preparation 5.

δ($CDCl_3$): 2.41 (m, 1H), 2.97 (s, 3H), 4.13 (m, 2H), 4.43 (m, 2H), 7.42 (m, 1H), 7.85 (m,1H), 8.00 (m, 1H), 8.70 (m, 1H).

PREPARATION 13 (Scheme 4)

6-(2-Hydroxyethyl)-3-methyl-4-pyridin-4-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (70%) from 3-methyl-4-pyridin-4-yl-6H-isoxazolo[3,4-d]pyridazin-7-one (V. Dal Piaz *et al., J. Pharmac. Sci.,* 1991, 80, 341-348) and 2-bromoethanol following the experimental procedure described in Preparation 5.

δ(DMSO-d_6): 2.60 (s, 3H), 3.78 (q, 2H), 4.18 (t, 2H), 4.83 (t, 1H), 7.68 (d, 2H), 8.78 (d, 2H).

PREPARATION 14 (Scheme 1)

5-Acetyl-4-amino-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

A mixture of the title compound of Preparation 5 (8.44 g, 33 mmol) and 10% palladium on charcoal (1.7 g) in ethanol (400 mL) was shaken under hydrogen at room temperature and 2 bar for 6 h. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (6.43 g, 76% yield).

$\delta(CDCl_3)$: 1.42 (t, 3H), 1.82 (s, 3H), 4.25 (q, 2H), 7.45 (m,1H), 7.80 (m,1H), 8.70 (m, 2H).

PREPARATION 15 (Scheme 1)

5-Acetyl-4-amino-2-ethyl-6-pyridin-2-ylpyridazin-3(2H)-one

Obtained after column chromatography purification (40%) from the title product of Preparation 6 following the procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.41 (t, 3H), 1.80 (s, 3H), 4.30 (q, 2H), 7.05 (bs, 2H), 7.38 (m, 1H), 7.82 (m, 2H), 8.62 (m, 1H).

PREPARATION 16 (Scheme 1)

5-Acetyl-4-amino-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained (92%) from the title product of Preparation 7 following the procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.37 (t, 3H), 1.82 (s, 3H), 4.24 (q, 2H), 7.44 (d, 2H), 8.70 (d, 2H).

PREPARATION 17 (Scheme 1)

5-Acetyl-4-amino-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

A mixture of the title compound of Preparation 9 (1.0 g, 3.50 mmol) , 10% palladium on charcoal (56 mg) and ammonium formate (3.97 g, 63 mmol) in methanol (30 mL) was refluxed for 2 hours. Then the catalyst was filtered off and the solvent was removed

under reduced pressure. The resulting residue was partitioned between dichloromethane and water and the organic layer was washed with water twice. It was dried and solvent removed under reduced pressure to yield the title compound (471 mg, 47%).

$\delta(CDCl_3)$: 0.45 (m, 4H), 1.37 (m, 1H), 1.81 (s, 3H), 4.02 (d, 2H), 7.40 (m,1H), 7.80 (m,1H), 8.72 (m, 2H).

PREPARATION 18 (Scheme 1)

5-Acetyl-4-amino-2-(cyclopropylmethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

Obtained (90%) from the title product of Preparation 9 following the procedure described in Preparation 17.

$\delta(CDCl_3)$: 0.45 (m, 4H), 1.38 (m, 1H), 1.80 (s, 3H), 4.03 (d, 2H), 7.01 (bs, 2H); 7.52 (m, 1H), 7.83 (m,2H), 8.62 (m, 1H).

PREPARATION 19 (Scheme 1)

5-Acetyl-4-amino-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained (96%) from the title product of Preparation 10 following the procedure described in Preparation 14.

$\delta(DMSO\text{-}d_6)$: 0.41 (m, 4H), 1.28 (m, 1H), 1.82 (s, 3H), 3.97 (d, 2H), 7.42 (d, 2H); 7.82 (bs, 2H), 8.65 (d, 2H).

PREPARATION 20 (Scheme 1)

5-Acetyl-4-amino-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

Obtained (50%) from the title product of Preparation 11 following the procedure described in Preparation 17. It was refluxed for 2 hours and then stirred at room temperature overnight.

$\delta(CDCl_3)$: 1.78 (s, 3H), 4.22 (m, 2H), 4.41 (m, 3H), 7.45 (m,1H), 7.80 (m, 1H), 8.78 (m,2H).

PREPARATION 21 (Scheme 1)

5-Acetyl-4-amino-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

Obtained (64%) from the title product of Preparation 12 following the procedure described in Preparation 17.

$\delta(CDCl_3)$: 1.78 (s, 3H), 4.13 (t, 2H), 4.40 (t, 2H), 7.10 (bs, 2H), 7.38 (m, 1H), 7.82 (m, 2H), 8.62 (m, 1H).

PREPARATION 22 (Scheme 1)

5-Acetyl-4-amino-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained (55%) from the title product of Preparation 13 following the procedure described in Preparation 14.

$\delta(DMSO\text{-}d_6)$: 1.82 (s, 3H), 3.75 (m, 2H), 4.18 (t, 2H), 4.81 (bs, 1H), 7.48 (d, 2H), 7.85 (bs, 1H), 8.63 (d, 2H).

PREPARATION 23 (Scheme 7)

Ethyl 5-methyl-4-(thien-2-ylcarbonyl)isoxazole-3-carboxylate

Obtained as a solid (50%) from 1-thiophen-2-yl-butane-1,3-dione (Gash, V.W.; *Can J. Chem.*, 1967, 45, 2109-12) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.15 (t, 3H), 2.55 (s, 3H), 4.20 (q, 2H), 7.20-7.70 (m, 3H).

PREPARATION 24 (Scheme 4)

3-Methyl-4-thien-2-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained as a solid (57%) from the title compound of Preparation 23 using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.78 (s, 3H), 7.18-7.59 (m, 3H), 9.62 (s, 1H).

PREPARATION 25 (Scheme 4)

6-Ethyl-3-methyl-4-thien-2-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (83%) from the title compound from Preparation 24 following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.41 (t, 3H), 2.78 (s, 3H), 4.28 (q, 2H), 7.18-7.59 (m, 3H).

PREPARATION 26 (Scheme 1)

5-Acetyl-4-amino-2-ethyl-6-thien-2-ylpyridazin-3(2H)-one

Obtained (50%) from the title product of Preparation 25 following the procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.41 (t, 3H), 1.98 (s, 3H), 4.22 (q, 2H), 7.10-7.41 (m, 3H).

PREPARATION 27 (Scheme 7)

Ethyl 4-(4-fluorobenzoyl)-5-methylisoxazole-3-carboxylate

Obtained (95%) from 1-(4-fluorophenyl)butane-1,3-dione (Joshi, K.C.; Pathak, V.N.; Garg, U. *J. Indian Chem. Soc.* 1983, *60*, 1074-1076) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.1 (t, 3H), 2.50 (s, 3H), 4.20 (q, 2H), 7.20 (m, 2H), 7.80 (m, 2H).

PREPARATION 28 (Scheme 4)

4-(4-Fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (87%) from the title compound of Preparation 27, using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.55 (s, 3H), 7.30 (m, 2H), 7.60 (m,2H).

PREPARATION 29 (Scheme 4)

6-Ethyl-4-(4-fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

To a suspension of the title compound of Preparation 28 (0.49 g, 2.0 mmol) and anhydrous potassium carbonate (0.55 g, 4.0 mmol) in dry dimethylformamide (5.3 mL) was added ethyl bromide (0.44 g, 4.03 mmol) and the resulting mixture heated at 110°C for 40 minutes. Then ice-water was added (30 mL) and the resulting precipitate collected by filtration to afford the title compound (0.47 g, 86%) as a yellow solid.

$\delta(CDCl_3)$: 1.40 (t, 3H), 2.58 (s, 3H), 4.23 (q, 2H), 7.20 (m,2H), 7.58 (m,2H).

PREPARATION 30 (Scheme 2)

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-nitropyridazin-3(2*H*)-one

To a stirred suspension of the title compound of Preparation 29 (0.5 g, 1.83 mmol) in a mixture of acetic acid (7.3 mL), water (7.3 mL) and nitric acid (2.5 mL), cerium ammonium nitrate (6.0 g, 11 mmol) was added portionwise during 40 min. Addition of ice-cold water gave a crude precipitate which was filtered and washed with cold water to yield the title product (45% yield).

$\delta(CDCl_3)$: 1.43 (t, 3H), 2.20 (s, 3H), 4.40 (q, 2H), 7.20 (m, 2H), 7.48 (m, 2H).

PREPARATION 31 (Scheme 7)

Ethyl 4-(3-fluorobenzoyl)-5-methylisoxazole-3-carboxylate

Obtained (79%) from 1-(3-fluorophenyl)butane-1,3-dione (Joshi, K.C.; Pathak, V.N.; Garg, U. *J. Indian Chem. Soc.* 1983, *60*, 1074-1076) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.10 (t, 3H), 2.60 (s, 3H), 4.15 (q, 2H), 7.30 (m, 4H).

PREPARATION 32 (Scheme 4)

4-(3-Fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one.

Obtained (81%) from the title compound of Preparation 31, following the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.60 (s, 3H), 7.3 (m, 4H), 9.90 (s, 1H).

PREPARATION 33 (Scheme 4)

6-Ethyl-4-(3-fluorophenyl)-3-methylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one

Obtained (84%) from the title compound from Preparation 32 following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.40 (t, 3H), 2.58 (s, 3H), 4.30 (q, 2H), 7.30 (m, 3H), 7.50 (m, 1H).

PREPARATION 34 (Scheme 4)

6-(Cyclopropylmethyl)-4-(3-fluorophenyl)-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (37%) from the title compound from Preparation 32 and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5. The product was purified by column chromatography.

$\delta(CDCl_3)$: 0.52 (m, 4H), 1.38 (m, 1H), 2.58 (s, 3H), 4.07 (d, 2H), 7.30 (m, 3H), 7.55 (m, 1H).

PREPARATION 35 (Scheme 4)

4-(3-Fluorophenyl)-6-isopropyl-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

To a stirred solution of the title compound of preparation 32 (2.0 g, 8.16 mmol) in 30 mL of dry THF, triphenylphosphine (2.16 g, 8.24 mmol) and isopropanol (0.68 mL, 8.97 mmol) were added. The mixture was cooled to 0ºC and then diethylazadicarboxylate (1.3 mL, 8.24 mmol) was added dropwise. The final mixture was let to warm up to room

temperature and the stirred for 24h. Finally solvent was removed and the final product was isolated by column chromatography in a 37% yield.

$\delta(CDCl_3)$: 1.38 (d, 6H), 2.58 (s, 3H), 5.41 (h, 1H), 7.32 (m, 3H), 7.52 (m, 1H).

PREPARATION 36 (Scheme 2)

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-nitropyridazin-3(2*H*)-one

Obtained (40%) from the title product of Preparation 33 following the experimental procedure described in Preparation 30.

$\delta(CDCl_3)$: 1.50 (t, 3H), 2.20 (s, 3H), 4.40 (q, 2H), 7.20 (m, 3H), 7.46 (m, 1H).

PREPARATION 37 (Scheme 2)

5-Acetyl-2-(cyclopropylmethyl)-6-(3-fluorophenyl)-4-nitropyridazin-3(2H)-one

Obtained (23%) from the title product of Preparation 34 following the experimental procedure described in Preparation 30.

$\delta(CDCl_3)$: 0.54 (m, 4H), 1.51 (m, 1H), 2.21 (s, 3H), 4.16 (d, 2H), 7.22 (m, 3H), 7.45 (m, 1H).

PREPARATION 38 (Scheme 2)

5-Acetyl-6-(3-fluorophenyl)-2-isopropyl-4-nitropyridazin-3(2H)-one

Obtained (40%) from the title product of Preparation 35 following the experimental procedure described in Preparation 30.

$\delta(CDCl_3)$: 1.44 (d, 6H), 2.20 (s, 3H), 5.45 (h, 1H), 7.16 (m, 3H), 7.50 (m, 1H).

PREPARATION 39 (Scheme 4)

4-(3-Chlorophenyl)-6-(cyclopropylmethyl)-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (97%) from 4-(3-chlorophenyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5. The product was purified by column chromatography.

LRMS: m/z 316 $(M+1)^+$.

PREPARATION 40 (Scheme 2)

5-Acetyl-6-(3-chlorophenyl)-2-(cyclopropylmethyl)-4-nitropyridazin-3(2H)-one

Obtained (21%) from the title product of Preparation 39 following the experimental procedure described in Preparation 30.

LRMS: m/z 348 $(M+1)^+$.

PREPARATION 41 (Scheme 7)

Ethyl 4-[ethoxy(oxo)acetyl]-5-methylisoxazole-3-carboxylate

To a well stirred solution of sodium methoxide (10.5 g, 0.15 mol) in 100 mL of dry ethanol, diethyl oxalate (21 mL, 0.15 mol) was added dropwise and the mixture was warmed to 45°C. Then dry acetone (45 mL, 0.60 mol) was added and after 30 min the final mixture was refluxed for 3 hours and stirred at room temperature overnight. Finally solvent was removed and 100 mL of fresh dry ethanol were added. The mixture was cooled to 0°C and a solution of ethyl chloro(hydroximino)acetate (27.2g, 0.18 mol) in 25 mL of dry ethanol was added dropwise. Then it was stirred at 0°C for 30 min and at room temperature for 3 days. Finally solvent was removed and the crude thus obtained was partitioned between ethyl acetate and water. It was dried and solvent removed to yield the desired product (90%) as an orange oil.

$\delta(CDCl_3)$: 1.39 (m, 6H), 2.68 (s, 3H), 4.40 (m, 4H).

PREPARATION 42 (Scheme 5)

Ethyl 3-methyl-7-oxo-6,7-dihydroisoxazolo[3,4-d]pyridazine-4-carboxylate

Obtained as a solid (57%) from the title compound of Preparation 41 using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 1.41 (t, 3H), 3.01 (s, 3H), 4.50 (q, 2H), 6.30 (s, 1H).

PREPARATION 43 (Scheme 5)

Ethyl 6-ethyl-3-methyl-7-oxo-6,7-dihydroisoxazolo[3,4-d]pyridazine-4-carboxylate

Obtained (90%) from the title compound of Preparation 42 following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.42 (m, 6H), 3.00 (s, 3H), 4.25 (q, 2H), 4.48 (q, 2H)

PREPARATION 44 (Scheme 6)

Ethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate

Obtained (98%) from the title product of Preparation 43 following the procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.38 (m, 6H), 2.30 (s, 3H), 4.22 (q, 2H), 4.42 (q, 2H),7.50 (bs, 2H).

PREPARATION 45 (Scheme 6)

Ethyl 4-acetyl-5-[(3-chlorophenyl)amino]-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate

A mixture of the title compound of Preparation 44 (506 mg, 2.0 mmol), 3-chlorophenylboronic acid (626 mg, 4.0 mmol), anhydrous cupric acetate (540 mg, 3.0 mmol), triethylamine (0.56 mL, 4.0 mmol) and activated molecular sieves (1.6 g, 4 Å) in dry dichloromethane (25 mL) was stirred under air exposure at room temperature for 48 h. The reaction was filtered and the solvent removed under reduced pressure. The resulting residue was recrystallized from ethyl acetate (202 mg, 64% yield).

δ($CDCl_3$): 1.38 (t, 3H), 1.42 (t, 3H), 2.01 (s, 3H), 4.42 (m, 4H), 6.97 (m, 1H), 7.16 (m, 1H), 7.35 (m, 2H), 7.05 (s, 1H).

PREPARATION 46 (Scheme 5)

6-Ethyl-3-methyl-7-oxo-6,7-dihydro-isoxazolo[3,4-d]pyridazine-4-carboxylic acid

To a stirred solution of the title compound of preparation 43 (2.73 g, 11 mmol) in 90 mL of a 2:1 methanol/THF mixture, a solution of lithium hydroxide (1.87 g, 45 mmol) in 6 mL of water was added dropwise. The final mixture was stirred at room temperature for 5 hours and then diluted with some water and acidified with HCl 2N. It was extracted with ethyl acetate, dried and solvent removed to yield (89%) the title product.

δ(DMSO-d_3): 1.35 (t, 3H), 2.98 (s, 3H), 4.15 (q, 2H).

PREPARATION 47 (Scheme 5)

4-(1,3-Benzoxazol-2-yl)-6-ethyl-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

To a 100°C pre-warmed suspension of PPSE (6g) in 10 mL of 1,2-dichlorobenzene, a solution of 2-aminophenol (0.48 g, 4.4 mmol) in 10 mL of 1,2-dichlorobenzene was added and the mixture was stirred for a while. Then the title compound of preparation 46 (1.08 g, 4.84 mmol) was added in portions and the mixture was refluxed overnight. Then it was let to cool down and poured onto ice-water vigorously stirring. It was neutralized with potassium carbonate and extracted with dichloromethane. The organic layer was dried and solvent removed to yield a crude product that was purified by column chromatography. The title product was isolated (44%).

δ($CDCl_3$): 1.42 (t, 3H), 3.25 (s, 3H), 4.38 (q, 2H), 7.41 (m, 2H), 7.70 (m, 1H), 7.82 (m, 1H).

PREPARATION 48 (Scheme 1)

5-Acetyl-4-amino-6-(1,3-benzoxazol-2-yl)-2-ethylpyridazin-3(2H)-one

Obtained (98%) from the title product of Preparation 47 following the procedure de-

scribed in Preparation 14.

PREPARATION 49

5-Acetyl-4-amino-2-ethyl-6-phenylpyridazin-3(2*H*)-one

A mixture of 6-ethyl-3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) (2.0 g, 7.83 mmol) and 10% palladium on charcoal (400 mg) in ethanol (400 ml) was shaken under hydrogen at room temperature and 2 bar for 3 h. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (1.97 g, 98% yield).

m.p. 150.8-152.7°C

δ($CDCl_3$): 1.43 (t, 3H), 1.67 (bs, 2H), 1.78 (s, 3H), 4.26 (q, 2H), 7.45 (s, 5H).

PREPARATION 50

5-Acetyl-4-amino-6-thiophen-2-yl-2H-pyridazin-3-one

Obtained (78%) from the title compound of Preparation 24 following the procedure described in Preparation 17.

δ($CDCl_3$): 2.00 (s, 3H), 7.07-7.50 (m, 3H).

PREPARATION 51

5-Acetyl-4-amino-2-cyclopropylmethyl-6-thiophen-2-yl-2H-pyridazin-3-one

Obtained (60%) from the title compound of Preparation 50 and cyclopropylmethyl bromide following the procedure described in Preparation 5.

δ($CDCl_3$): 0.42-0.62 (m, 4H), 1.40 (m, 1H), 1.99 (s, 3H), 4.06 (d, 2H), 7.04-7.50 (m, 3H).

PREPARATION 52

Ethyl 5-methyl-4-(thien-3-ylcarbonyl)isoxazole-3-carboxylate

Obtained as a solid (70%) from 1-thiophen-3-yl-butane-1,3-dione (Harris, J; Levine, H; *J. Am. Chem. Soc.,* 1948, 70, 3360) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.17 (t, 3H), 2.58 (s, 3H), 4.20 (q, 2H), 7.36-7.70 (m, 3H).

PREPARATION 53

3-Methyl-4-thien-3-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained as a solid (38%) from the title compound of Preparation 52 using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.60 (s, 3H), 7.36-8.00 (m, 3H), 12.62 (s, 1H).

PREPARATION 54

6-Ethyl-3-methyl-4-thien-3-ylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (71%) from the title compound from Preparation 53 following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.42 (t, 3H), 2.67 (s, 3H), 4.26 (q, 2H), 7.30-7.62 (m, 3H).

PREPARATION 55

5-Acetyl-4-amino-2-ethyl-6-thien-3-ylpyridazin-3(2H)-one

Obtained (84%) from the title product of Preparation 54 following the procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.41 (t, 3H), 1.88 (s, 3H), 4.26 (q, 2H), 7.17-7.48 (m, 3H).

PREPARATION 56

6-Ethyl-4-phenyl-3-styryl-6H-isoxazolo[3,4-d]pyridazin-7-one

To a freshly prepared solution of sodium methoxide (108 mg, 1.96 mmol) in methanol (2 ml), a solution of 6-ethyl-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one (500 mg, 1.96 mmol) (Dal Piaz, V.; Giovannoni, M.P.; Castellana, C.; *et al* ,*J. Med. Chem.* **1997**, 40, 1417-1421) in of dry methanol (2 ml) was added and the mixture was stirred for a while. Then, benzaldehyde (0.40 ml, 3.92 mmol) was added dropwise and the final mixture was refluxed for 2 hours. The resulting suspension was let to cool down and the final product (514 mg, 76% yield) was collected by filtration.

$\delta(CDCl_3)$: 1.40 (t, 3H), 4.31 (q, 2H), 6.80 (d, 1H), 7.35 (m, 5H), 7.68 (m, 6H).

PREPARATION 57

6-Ethyl-4-phenyl-3-(2-thiophen-3-yl-vinyl)-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained (75%) from 6-ethyl-3-methyl-4-phenyl-6H-isoxazolo[3,4-d]pyridazin-7-one (500 mg, 1.96 mmol) (Dal Piaz, V.; Giovannoni, M.P.; Castellana, C.; *et al* ,*J. Med. Chem.* 1997, *40*, 1417-1421) and thiophene-3-carbaldehyde following the procedure described in Preparation 56.

$\delta(CDCl_3)$: 1.42 (t, 3H), 4.30 (q, 2H), 6.58 (d, 1H), 6.98 (d, 1H), 7.28 (m, 1H), 7.42 (m, 1H), 7.63 (m, 6H).

PREPARATION 58

4-Amino-2-ethyl-6-phenyl-5-(3-phenylpropionyl)pyridazin-3(2H)-one

A mixture of the title compound of preparation 56 (514 mg, 1.50 mmol) and 10% palladium on charcoal (100 mg) in ethanol (100 ml) was shaken under hydrogen at room temperature and 2 bar overnight. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (487 mg, 95% yield).

m.p. 115.1-116.1°C

$\delta(CDCl_3)$: 1.40 (t, 3H), 2.28 (t, 2H), 2.68 (t, 2H), 4.25 (q, 2H), 6.78 (m, 2H), 7.05 (m, 3H), 7.45 (m, 5H).

PREPARATION 59

4-Amino-2-ethyl-6-phenyl-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one

Obtained (67%) from the title compound of Preparation 57 following the procedure described in Preparation 58.

$\delta(CDCl_3)$: 1.41 (t, 3H), 2.30 (t, 2H), 2.70 (t, 2H), 4.25 (q, 2H), 6.08 (d, 1H), 6.54-6.62 (m, 2H), 7.08-7.58 (m, 7H).

PREPARATION 60

4-(Benzofuran-2-carbonyl)-5-methyl-isoxazole-3-carboxylic acid ethyl ester

Obtained as a solid (80%) from 1-benzofuran-2-yl-butane-1,3-dione (Richard, F.; Carreyre, H.; Coustard, J. M.; Bachmann, C.; Perot, G., *Tetrahedron* 1998, 54(49), 14757-14766) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.10 (t, 3H), 2.21 (s, 3H), 4.15 (q, 2H), 7.16-7.80 (m, 5H).

PREPARATION 61

4-Benzofuran-2-yl-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (65%) from the title compound of Preparation 60 using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.99 (s, 3H), 7.29-7.49 (m, 3H), 7.70-7080 (m, 2H).

PREPARATION 62

4-Benzofuran-2-yl-6-ethyl-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained (67%) from the title compound from Preparation 61 following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.44 (t, 3H), 3.07 (s, 3H), 4.32 (q, 2H), 7.27-7.76 (m, 5H).

PREPARATION 63

5-Acetyl-4-amino-6-benzofuran-2-yl-2-ethyl-2H-pyridazin-3-one

Obtained (90%) from the title product of Preparation 62 following the procedure described in Preparation 17.

$\delta(CDCl_3)$: 1.44 (t, 3H), 1.99 (s, 3H), 4.27 (q, 2H), 7.16 (s, 1H), 7.27-7.72 (m, 6H).

PREPARATION 64

6-(Cyclopropylmethyl)-4-(4-fluorophenyl)-3-methylisoxazolo[3,4-d]pyridazin-7(6H)-one

Obtained (46%) from the title compound from Preparation 28 and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5. The product was purified by column chromatography.

$\delta(CDCl_3)$: 0.54 (m, 4H), 1.38 (m, 1H), 2.58 (s, 3H), 4.08 (d, 2H), 7.28 (d, 2H), 7.57 (dd, 2H).

PREPARATION 65

5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-nitropyridazin-3(2H)-one

Obtained (37%) from the title product of Preparation 64 following the experimental procedure described in Preparation 30.

$\delta(CDCl_3)$: 0.46 (m, 2H), 0.62 (m, 2H), 1.45 (m, 1H), 2.21 (s, 3H), 4.18 (d, 2H), 7.21 (m, 2H), 7.45 (m, 2H).

PREPARATION 66

4-Nitro-[2,7]naphthyridin-1-ol

To a stirred solution of 2H-[2,7]naphthyridin-1-one (300 mg, 2.05 mmol) (Baldwin, J. J.; Mensler, K.; Ponticello, G. S, *J. Org. Chem.* 1978, 43(25), 4878-80.) in 98% sulfuric acid (2 ml), 60% nitric acid (0.30 ml) was added dropwise and the mixture

was warmed to 85ºC during 3 h. Addition of ice-cold water and basification to pH 7 gave a precipitate which was filtered and washed with ethyl ether to yield the title product as a yellow solid (87%).

δ(DMSO-d6): 8.23 (d, 1H), 8.60 (d, 1H), 8.88 (s, 1H), 9.18 (d, 1H).

PREPARATION 67

4-Amino-[2,7]naphthyridin-1-ol

A mixture of the title compound of Preparation 66 (100 mg; 0.52 mmol) and Ni-Raney (10 mg) in methanol (15 ml) was shaken under hydrogen at room temperature and 1 atm overnight . Then catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (100%).

LRMS: m/Z 162 $(M+1)^+$

PREPARATION 68

4-(4-Methoxy-benzoyl)-5-methyl-isoxazole-3-carboxylic acid ethyl ester

Obtained as a yellow oil (63%) from 1-(4-methoxy-phenyl)-butane-1,3-dione (Popic,V.V. *et al.*, *Synthesis* **1991** *(3)*, 195) and ethyl chloro(hydroximino)acetate following the experimental procedure described in Preparation 1.The final product was purified by column cromatography (n-Hex/EtOAc 9:1 to 1:1).

δ($CDCl_3$): 1.18 (t, 3H), 2.58 (s, 3H), 3.90 (s, 3H), 4.20 (q, 2H), 6.95 (d, 2H), 7.80 (d, 2H).

PREPARATION 69

4-(4-Methoxy-phenyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a white solid (91%) from the title compound of Preparation 68 using the experimental procedure described in Preparation 3.

δ($DMSO-d_6$): 2.54 (s, 3H), 3.84 (s, 3H), 7.09 (d, 2H), 7.56 (d, 2H).

LRMS (m/z): 258 $(M+1)^+$.

PREPARATION 70

6-Ethyl-4-(4-methoxyphenyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a yellow solid (79%) from the title compound from Preparation 69 following the experimental procedure described in Preparation 5.

δ(DMSO-d_6): 1.30 (t, 3H), 2.57 (s, 3H), 3.84 (s, 3H), 4.13 (q, 2H), 7.10 (d, 2H), 7.60 (d, 2H).

LRMS (m/z): 286 $(M+1)^+$.

PREPARATION 71

5-Acetyl-4-amino-2-ethyl-6-(4-methoxy-phenyl)-2H-pyridazin-3-one

Obtained (84%) from the title product of Preparation 70 following the procedure described in Preparation 14.

δ(DMSO-d_6): 1.29 (t, 3H), 1.75 (s, 3H), 3.81 (s, 3H), 4.10 (q, 2H), 7.03 (d, 2H), 7.35 (d, 2H).

PREPARATION 72

4-(3-Methoxy-benzoyl)-5-methyl-isoxazole-3-carboxylic acid ethyl ester

The title compound was synthesized (76%) from 1-(3-methoxy-phenyl)-butane-1,3-dione (Popic,V.V. *et al., Synthesis* **1991** *(3)*, 195) following the procedure described in Preparation 1.

δ(DMSO-d_6): 1.00 (t, 3H), 2.57 (s, 3H), 3.8 (s, 3H), 4.08 (q, 2H), 7.25-7.35 (m, 3H), 7.45 (m, 1H).

PREPARATION 73

4-(3-Methoxy-phenyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (69%) from the title compound of Preparation 72 using the experimental procedure described in Preparation 3.

δ(DMSO-d_6): 2.57 (s, 3H), 3.82 (s, 3H), 7.10 (d, 1H), 7.15-7.20 (m, 2H), 7.45 (t, 1H), 12.75 (s, *NH*).

PREPARATION 74

6-Ethyl-4-(3-methoxy-phenyl)-3-methyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (80%) from the title compound of Preparation 73 using the experimental procedure described in Preparation 5.

δ(DMSO-d_6): 1.35 (t, 3H), 2.57 (s, 3H), 3.82 (s, 3H), 4.15 (q, 2H), 7.10-7.25 (m, 3H), 7.45 (t, 1H).

PREPARATION 75

5-Acetyl-4-amino-2-ethyl-6-(3-methoxy-phenyl)-2H-pyridazin-3-one

Obtained as a solid (72%) from the title compound of Preparation 74 using the experimental procedure described in Preparation 14.

δ(DMSO-d_6): 1.35 (t, 3H), 1.78 (s, 3H), 3.82 (s, 3H), 4.10 (q, 2H), 6.90-7.10 (m, 3H), 7.40 (t, 1H), 7.78 (bs, 2H, NH_2).

PREPARATION 76

5-Methyl-4-(4-methyl-benzoyl)-isoxazole-3-carboxylic acid ethyl ester

The title compound was synthesized (83%) from 1-p-tolyl-butane-1,3-dione (Popic,V.V. *et al.*, *Synthesis* **1991** *(3)*, 195) following the procedure described in Preparation 1.

δ($CDCl_3$): 1.10 (t, 3H), 2.42 (s, 3H), 2.58 (s, 3H), 4.18 (q, 2H), 7.30 (d, 2H), 7.70 (d, 2H).

PREPARATION 77

3-Methyl-4-p-tolyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (38%) from the title compound of Preparation 76 using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.48 (s, 3H), 2.58 (s, 3H), 7.35 (d, 2H), 7.42 (d, 2H).

PREPARATION 78

6-Ethyl-3-methyl-4-p-tolyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (89%) from the title compound of Preparation 77 using the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.42 (t, 3H), 2.48 (s, 3H), 2.58 (s, 3H), 4.30 (q, 2H), 7.35 (d, 2H), 7.45 (d, 2H).

LRMS (m/z): 270 $(M+1)^+$.

Retention Time: 9.60 min.

PREPARATION 79

5-Acetyl-4-amino-2-ethyl-6-p-tolyl-2H-pyridazin-3-one

Obtained as a solid (91%) from the title compound of Preparation 78 using the experimental procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.42 (t, 3H), 1.80 (s, 3H), 2.42 (s, 3H), 4.28 (q, 2H), 7.30 (d, 2H), 7.38 (d, 2H).

LRMS (m/z): 272 $(M+1)^+$.

Retention Time: 9.27 min.

PREPARATION 80

5-Methyl-4-(3-methyl-benzoyl)-isoxazole-3-carboxylic acid ethyl ester

The title compound was synthesized (73%) from 1-m-tolyl-butane-1,3-dione (Popic,V.V. *et al.*, *Synthesis* **1991** *(3)*, 195) following the procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.10 (t, 3H), 2.40 (s, 3H), 2.58 (s, 3H), 4.15 (q, 2H), 7.30-7.50 (m, 3H), 7.58 (m, 1H).

PREPARATION 81

3-Methyl-4-*m*-tolyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (73%) from the title compound of Preparation 80 using the experimental procedure described in Preparation 3.

$\delta(CDCl_3)$: 2.45 (s, 3H), 2.58 (s, 3H), 7.30-7.50 (m, 4H), 10.05 (bs, 1H, *NH*).

PREPARATION 82

6-Ethyl-3-methyl-4-*m*-tolyl-6H-isoxazolo[3,4-d]pyridazin-7-one

Obtained as a solid (88%) from the title compound of Preparation 81 using the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 1.42 (t, 3H), 2.45 (s, 3H), 2.58 (s, 3H), 4.30 (q, 2H), 7.30-7.50 (m, 4H).

PREPARATION 83

5-Acetyl-4-amino-2-ethyl-6-*m*-tolyl-2H-pyridazin-3-one

Obtained as a solid (80%) from the title compound of Preparation 82 using the experimental procedure described in Preparation 14.

$\delta(CDCl_3)$: 1.42 (t, 3H), 1.80 (s, 3H), 2.42 (s, 3H), 4.28 (q, 2H), 7.20-7.40 (m, 4H).

LRMS (m/z): 272 $(M+1)^+$.

Retention Time: 9.25 min.

PREPARATION 84

4-(3-Oxo-butyryl)-benzoic acid methyl ester

A solution of dimethyl terephthalate (10 g, 51.5 mmole) and acetone (4.15 mL, 56.6 mmole) in a mixture of toluene/dimethoxyethane (75mL/25 mL) was added to a suspension of NaH 60% (2.68 g, 66.9 mmole) in dry toluene (25 mL) under argon. The mixture was heated at 100 °C for 4 hours. The reaction mixture was cooled to rt and 25 mL of water were added. The pH was adjusted to 3-4 with HCl 2N and the mixture was poured into water (300 mL). The aqueous mixture was extracted with ethyl acetate (3x150 mL), dried over sodium sulphate and evaporated to afford a yellow solid which was purified by column cromatography (n-Hex/EtOAc 9:1 to 7:3) to afford the title compound (2.78 g, 25% yield) as a yellow solid.

$\delta(CDCl_3)$: 2.25 (s, 3H), 3.95 (s, 3H), 6.20 (s, 1H), 7.90 (d, 2H), 8.10 (d, 2H).

LRMS (m/z): 221 $(M+1)^+$.

Retention Time: 9.42 min.

PREPARATION 85

4-(4-Methoxycarbonyl-benzoyl)-5-methyl-isoxazole-3-carboxylic acid ethyl ester

The title compound was synthesized (64%) from the title compound of Preparation 84 following the procedure described in Preparation 1.

$\delta(CDCl_3)$: 1.10 (t, 3H), 2.58 (s, 3H), 3.98 (s, 3H), 4.18 (q, 2H), 7.80 (d, 2H), 8.15 (d, 2H).

PREPARATION 86

4-(3-Methyl-7-oxo-6,7-dihydro-isoxazolo[3,4-d]pyridazin-4-yl)-benzoic acid methyl ester

Obtained as a solid (91%) from the title compound of Preparation 85 using the experimental procedure described in Preparation 3.

δ($CDCl_3$): 2.58 (s, 3H), 3.98 (s, 3H), 7.62 (d, 2H), 8.20 (d, 2H), 9.85 (bs, 1H, *NH*).

PREPARATION 87

4-(6-Ethyl-3-methyl-7-oxo-6,7-dihydro-isoxazolo[3,4-d]pyridazin-4-yl)-benzoic acid methyl ester

Obtained as a solid (70%) from the title compound of Preparation 86 using the experimental procedure described in Preparation 5.

δ($CDCl_3$): 1.42 (t, 3H), 2.58 (s, 3H), 3.98 (s, 3H), 4.30 (q, 2H), 7.62 (d, 2H), 8.20 (d, 2H).

PREPARATION 88

4-(4-Acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid methyl ester

Obtained as a solid (97%) from the title compound of Preparation 87 using the experimental procedure described in Preparation 14.

δ($CDCl_3$): 1.42 (t, 3H), 1.78 (s, 3H), 3.96 (s, 3H), 4.26 (q, 2H), 7.55 (d, 2H), 8.14 (d, 2H).

LRMS (m/z): 316 $(M+1)^+$.

Retention Time: 8.80 min.

PREPARATION 89

3-(3-Oxo-butyryl)-benzoic acid methyl ester

A solution of dimethyl isophthalate (12 g, 61.85 mmole) and acetone (5 mL, 68 mmole) in a mixture of toluene/dimethoyethane (90mL/30 mL) was added to a suspension of NaH 60% (2.97 g, 74.23 mmole) in dry toluene (30 mL) under argon. The mixture was heated at 100 °C for 4 hours. The reaction mixture was cooled to rt and 25 mL of water were added. The mixture was poured into water (250 mL) and the pH was adjusted to 3-4 with HCl 2N. The aqueous mixture was extracted with ethyl acetate (2x250 mL),

washed with brine, dried over sodium sulphate and evaporated to afford a yellow solid which was purified by column cromatography (n-Hex/EtOAc 9:1 to 8:2) to afford the title compound (1.78 g, 11% yield) as a yellow solid.

δ($CDCl_3$): 2.23 (s, 3H), 3.96 (s, 3H), 6.25 (s, 1H), 7.57 (d, 1H), 8.20 (m, 2H), 8.51 (s, 1H).

LRMS (m/z): 221 $(M+1)^+$.

Retention Time: 9.32 min.

PREPARATION 90

4-(3-Methoxycarbonyl-benzoyl)-5-methyl-isoxazole-3-carboxylic acid ethyl ester

The title compound was synthesized (62%) from the title compound of Preparation 89 following the procedure described in Preparation 1.

LRMS (m/z): 318 $(M+1)^+$.

Retention Time: 9.07 min.

PREPARATION 91

3-(3-Methyl-7-oxo-6,7-dihydro-isoxazolo[3,4-d]pyridazin-4-yl)-benzoic acid methyl ester

Obtained as a solid (80%) from the title compound of Preparation 90 using the experimental procedure described in Preparation 3.

LRMS (m/z): 286 $(M+1)^+$.

Retention Time: 7.73 min.

PREPARATION 92

3-(6-Ethyl-3-methyl-7-oxo-6,7-dihydro-isoxazolo[3,4-d]pyridazin-4-yl)-benzoic acid methyl ester

Obtained as a solid (99%) from the title compound of Preparation 91 using the experimental procedure described in Preparation 5.

δ($CDCl_3$): 1.42 (t, 3H), 2.58 (s, 3H), 3.96 (s, 3H), 4.26 (q, 2H), 7.65 (dd, 1H), 7.80 (d, 1H), 8.20 (d, 1H), 8.25 (s, 1H).

LRMS (m/z): 314 $(M+1)^+$.

Retention Time: 9.02 min.

PREPARATION 93

3-(4-Acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzoic acid methyl ester

Obtained as a solid (98%) from the title compound of Preparation 92 using the experimental procedure described in Preparation 14.

δ($CDCl_3$): 1.42 (t, 3H), 1.78 (s, 3H), 3.96 (s, 3H), 4.26 (q, 2H), 7.45-7.70 (m, 4H), 8.15 (d, 1H), 8.18 (s, 1H).

LRMS (m/z): 316 $(M+1)^+$.

Retention Time: 8.68 min.

PREPARATION 94

(3-Methyl-7-oxo-4-phenyl-7H-isoxazolo[3,4-d]pyridazin-6-yl)-acetic acid methyl ester

Obtained as a white solid (89%) from 3-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one (Renzi, G.; Pinzauti, S.; *Il Farmaco Ed. Sci.* **1969**, *24*, 885-889) and methyl bromoacetate following the experimental procedure described in Preparation 5.

δ($CDCl_3$): 2.55 (s, 3H), 3.78 (s, 3H), 4.98 (s, 2H), 7.57 (m, 5H).

PREPARATION 95

(4-Acetyl-5-amino-6-oxo-3-phenyl-6H-pyridazin-1-yl)-acetic acid methyl ester

Obtained as a white solid (99%) from the title compound of Preparation 94 following the experimental procedure described in Preparation 14.

δ($CDCl_3$): 1.80 (s, 3H), 3.80 (s, 3H), 4.92 (s, 2H), 7.42 (m, 5H).

PREPARATION 96

6-Cyclopropylmethyl-3-methyl-4-phenyl-6H-isoxazolo[3,4d]pyridazin-7-one

Obtained (91%) from 3-methyl-4-phenyl-6H-isoxazolo[3,4d]pyridazin-7-one (Dal Piaz, V. et al. *J. Med. Chem.* 1997, 40, 1417) and cyclopropylmethyl bromide following the experimental procedure described in Preparation 5.

$\delta(CDCl_3)$: 0.50 (m, 4H), 1.4 (m, 1H), 2.50 (s, 3H), 4.10 (q, 2H), 7.50 (m, 5H).

PREPARATION 97

5-Acetyl-2-cyclopropylmethyl-4-nitro-6-phenyl-2H-pyridazin-3-one.

Obtained (15.4%) from the title compound of Preparation 96 following the experimental procedure described in Preparation 30. The crude was purified by column chromatography (silica gel, hexane/ethyl acetate 8:1).

$\delta(CDCl_3)$: 0.50 (m, 2H), 0.70 (m, 2H), 1.4 (m, 1H), 2.20 (s, 3H), 4.20 (q, 2H), 7.50 (m, 5H).

PREPARATION 98

5-Nitroquinoline-8-carboxilic acid methyl ester.

To a stirred solution of 300 mg (1.375 mmol) of 5-nitroquinoline-8-carboxilic acid (Breckenridge, J. G. Et al., *Canadian J. of Research Sect. B;* 1947, 25, 49) in DMF (6 mL), 546 mg (3.850 mmol) of iodomethane and 190 mg (1.375 mmol) of potassium carbonate were added. The resulting mixture was stirred at room temperature for one hour. Water (10 mL) was added and the product collected by filtration. The residue was washed with water and dried to yield the title compound (250 mg, 78.4 %).

LRMS: m/Z 233 $(M+1)^+$

$\delta(CDCl_3)$: 4.05 (s, 3H), 7.70 (m, 1H), 8.00 (d, 1H), 8.30 (d, 1H), 9.00 (d, 1H), 9.15 (m, 1H).

PREPARATION 99

5-Aminoquinoline-8-carboxilic acid methyl ester.

A mixture of the title compound of Preparation 98 (100 mg, 0.431 mmol) and 10 % palladium on charcoal (46 mg) in ethanol (5 mL) was shaken under hydrogen at room temperature and 1 bar for 15 minutes. The catalyst was filtered off and the solvent removed under reduced pressure to yield the title compound (84 mg, 96 %)

LRMS: m/Z 203 $(M+1)^+$

EXAMPLES

In the following tables some acronyms have been used with the following meanings:

Acronym	Meaning
2-Pyr	2-pyridyl
3-Pyr	3-pyridyl
4-Pyr	4-pyridyl
Ph	Phenyl
(2-F)Ph	2-fluorophenyl
(3-F)Ph	3-fluorophenyl
(4-F)Ph	4-fluorophenyl
(2-Cl)Ph	2-chlorophenyl
(3-Cl)Ph	3-chlorophenyl
(2-Me)Ph	2-methylphenyl or o-tolyl
(3-Me)Ph	3-methylphenyl or m-tolyl
(4-Me)Ph	4-methylphenyl or p-tolyl
(2-MeO)Ph	2-methoxyphenyl
(3-MeO)Ph	3-methoxyphenyl
(4-MeO)Ph	4-methoxyphenyl
(3-CO_2Me)Ph	3-methoxycarbonylphenyl
(4-CO_2Me)Ph	4-methoxycarbonylphenyl
(4-CO_2H)Ph	4-hydroxycarbonylphenyl
(4-CH_2OH)Ph	4-hydroxymethylphenyl
(3-CN)Ph	3-cyanophenyl
(4-CN)Ph	4-cyanophenyl
(3-NO_2)Ph	3-nitrophenyl
1-Naph	1-naphtyl
(3,5-diCl)Ph	3,5-dichlorophenyl
$C_3H_5CH_2$	cyclopropylmethyl

In addition in formulas of radicals R3 or R5 depicted in the tables the simbol X does not simbolise any atoms and has only been used to simbolise the point of attachment of the radicals.

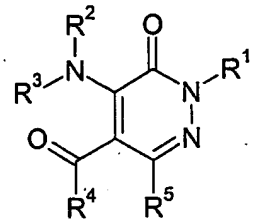


Table 2

Example	R1	R2	R3	R4	R5
1	Et	H	(3-F)Ph	Me	3-Pyr
2	Et	H	(3-Cl)Ph	Me	3-Pyr
3	Et	H	(3,5-diCl)Ph	Me	3-Pyr
4	Et	H	1-Naph	Me	3-Pyr
5	Et	H	(4-CO_2Me)Ph	Me	3-Pyr
6	Et	H	(2-F)Ph	Me	3-Pyr

Example	R1	R2	R3	R4	R5
7	Et	H	(2-Cl)Ph	Me	3-Pyr
8	Et	H	(4-CH_2OH)Ph	Me	3-Pyr
9	Et	H	(3-CN)Ph	Me	3-Pyr
10	$C_3H_5CH_2$	H	(3-Cl)Ph	Me	3-Pyr
11	$C_3H_5CH_2$	H	(3,5-diCl)Ph	Me	3-Pyr
12	$C_3H_5CH_2$	H	(2-F)Ph	Me	3-Pyr
13	$C_3H_5CH_2$	H	(2-Cl)Ph	Me	3-Pyr
14	$C_3H_5CH_2$	H	(3-CN)Ph	Me	3-Pyr

Example	R1	R2	R3	R4	R5
15	$HOCH_2CH_2$	H	(4-CO_2Me)Ph	Me	3-Pyr
16	$HOCH_2CH_2$	H	(2-F)Ph	Me	3-Pyr
17	$HOCH_2CH_2$	H	(2-Cl)Ph	Me	3-Pyr
18	$HOCH_2CH_2$	H	(3-Cl)Ph	Me	3-Pyr
19	Et	H	(3-Cl)Ph	Me	2-Pyr
20	Et	H	(3-CN)Ph	Me	2-Pyr
21	Et	H	(4-CH_2OH)Ph	Me	2-Pyr
22	$C_3H_5CH_2$	H	(3-CN)Ph	Me	2-Pyr

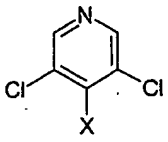
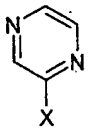
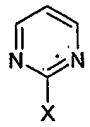
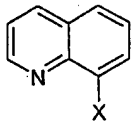
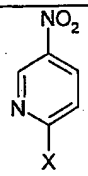
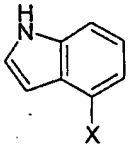
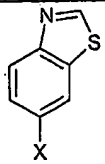
Example	R1	R2	R3	R4	R5
23	$C_3H_5CH_2$	H	(3-Cl)Ph	Me	2-Pyr
24	$C_3H_5CH_2$	H	(4-CH_2OH)Ph	Me	2-Pyr
25	$C_3H_5CH_2$	H	(3,5-diCl)Ph	Me	2-Pyr
26	$HOCH_2CH_2$	H	(3-CN)Ph	Me	2-Pyr
27	$HOCH_2CH_2$	H	(3-Cl)Ph	Me	2-Pyr
28	$HOCH_2CH_2$	H	(3,5-diCl)Ph	Me	2-Pyr
29	$HOCH_2CH_2$	H	(4-CH_2OH)Ph	Me	2-Pyr
30	Et	H	(3-F)Ph	Me	4-Pyr

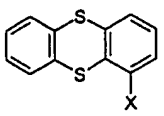
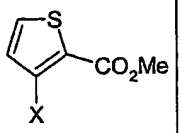
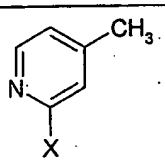
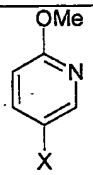
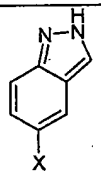
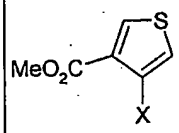
Example	R1	R2	R3	R4	R5
31	Et	H	(3-Cl)Ph	Me	4-Pyr
32	Et	H	1-Naph	Me	4-Pyr
33	Et	H	(2-Me)Ph	Me	4-Pyr
34	Et	H	(4-CO_2Me)Ph	Me	4-Pyr
35	Et	H	(2-MeO)Ph	Me	4-Pyr
36	Et	H	(3-MeO)Ph	Me	4-Pyr
37	Et	H	(2-F)Ph	Me	4-Pyr
38	Et	H	(2-Cl)Ph	Me	4-Pyr

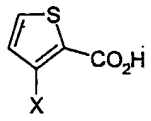
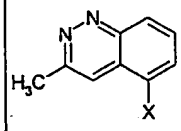
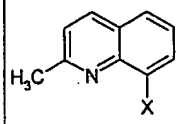
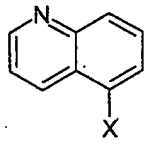
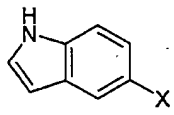
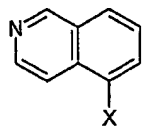
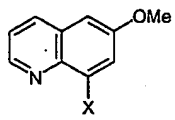
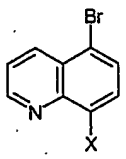
Example	R1	R2	R3	R4	R5
39	Et	H	(3-CN)Ph	Me	4-Pyr
40	Et	H	(4-CH_2OH)Ph	Me	4-Pyr
41	Et	H	(4-CO_2H)Ph	Me	4-Pyr
42	$C_3H_5CH_2$	H	(2-F)Ph	Me	4-Pyr
43	$C_3H_5CH_2$	H	(2-Cl)Ph	Me	4-Pyr
44	$C_3H_5CH_2$	H	(3-CN)Ph	Me	4-Pyr
45	$C_3H_5CH_2$	H	(4-CH_2OH)Ph	Me	4-Pyr
46	$C_3H_5CH_2$	H	(3-Cl)Ph	Me	4-Pyr

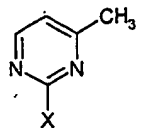
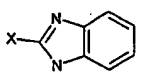
Example	R1	R2	R3	R4	R5
47	$HOCH_2CH_2$	H	(2-F)Ph	Me	4-Pyr
48	$HOCH_2CH_2$	H	(2-Cl)Ph	Me	4-Pyr
49	$HOCH_2CH_2$	H	(3-CN)Ph	Me	4-Pyr
50	$HOCH_2CH_2$	H	(4-CH_2OH)Ph	Me	4-Pyr
51	$HOCH_2CH_2$	H	(3-Cl)Ph	Me	4-Pyr
52	Et	H	(3-Cl)Ph	Me	2-Thienyl
53	Et	(3-F)Ph	(3-F)Ph	Me	3-Pyr
54	Et	(4-CO_2Me)Ph	(4-CO_2Me)Ph	Me	3-Pyr

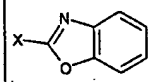
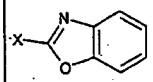
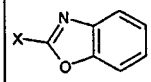
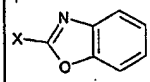
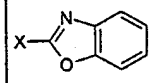
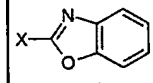
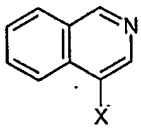
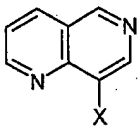
Example	R1	R2	R3	R4	R5
55	Et	(4-CH_2OH)Ph	(4-CH_2OH)Ph	Me	3-Pyr
56	Et	(3-NO2)Ph	(3-NO2)Ph	Me	4-Pyr
57	Et	(3-F)Ph	(3-F)Ph	Me	4-Pyr
58	$C_3H_5CH_2$	(3-Cl)Ph	(3-Cl)Ph	Me	3-Pyr
59	$C_3H_5CH_2$	(3,5-diCl)Ph	(3,5-diCl)Ph	Me	3-Pyr
60	$HOCH_2CH_2$	(4-CO_2Me)Ph	(4-CO_2Me)Ph	Me	3-Pyr
61	$HOCH_2CH_2$	(3-Cl)Ph	(3-Cl)Ph	Me	2-Pyr
62	$C_3H_5CH_2$	(3-Cl)Ph	(3-Cl)Ph	Me	4-Pyr

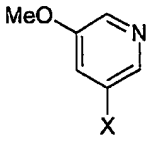
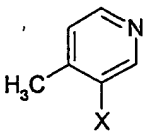
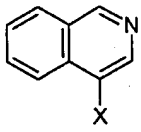
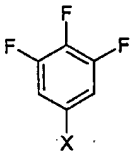
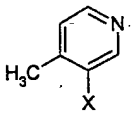
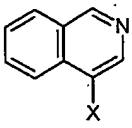
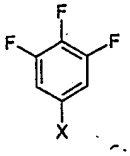
Example	R1	R2	R3	R4	R5
63	Et	H	3-Pyr	Me	Ph
64	Et	H		Me	Ph
65	Et	H		Me	Ph
66	Et	H		Me	Ph
67	Et	H		Me	Ph
68	Et	H		Me	Ph
69	Et	H		Me	Ph
70	Et	H		Me	Ph

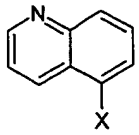
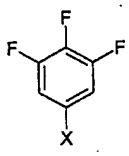
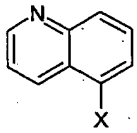
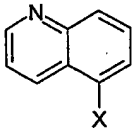
Example	R1	R2	R3	R4	R5
71	Et	H		Me	Ph
72	Et	H		Me	Ph
73	Et	H		Me	Ph
74	Et	H		Me	Ph
75	Et	H		Me	Ph
76	Et	H		Me	Ph
77	Et	H		Me	Ph
78	Et	H	2-Pyr	Me	Ph

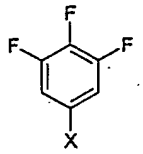
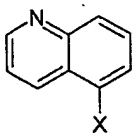
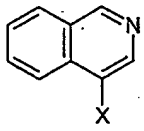
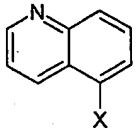
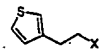
Example	R1	R2	R3	R4	R5
79	Et	H		Me	Ph
80	Et	H		Me	Ph
81	Et	H		Me	Ph
82	Et	H		Me	Ph
83	Et	H		Me	Ph
84	Et	H		Me	Ph
85	Et	H		Me	Ph
86	Et	H		Me	Ph

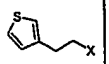
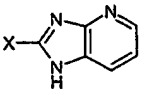
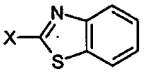
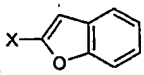
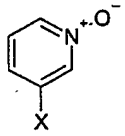
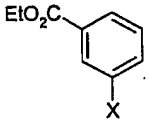
Example	R1	R2	R3	R4	R5
87	Et	H		Me	Ph
88	Et	H	3-Pyr	Me	(3-Cl)Ph
89	C3H5CH2	H	3-Pyr	Me	(3-Cl)Ph
90	Et	H	3-Pyr	Me	(3-F)Ph
91	iPr	H	3-Pyr	Me	(3-F)Ph
92	C3H5CH2	H	3-Pyr	Me	(3-F)Ph
93	Et	H	3-Pyr	Me	(4-F)Ph
94	Et	H	(3-Cl)Ph	Me	

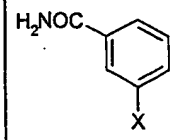
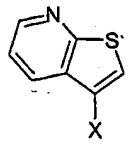
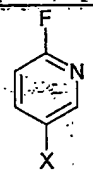
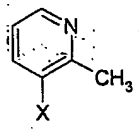
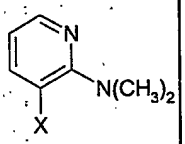
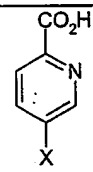
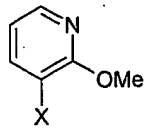
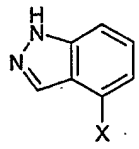
Example	R1	R2	R3	R4	R5
95	Et	H	(3-Cl)Ph	Me	
96	Et	H	(3-F)Ph	Me	
97	Et	(3-Cl)Ph	(3-Cl)Ph	Me	
98	Et	(3-F)Ph	(3-F)Ph	Me	
99	Et	H	(3-MeO)Ph	Me	
100	Et	H	(4-CH2OH)Ph	Me	
101	Et	H		Me	Ph
102	Et	H		Me	Ph

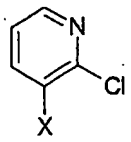
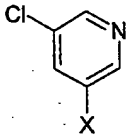
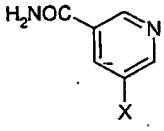
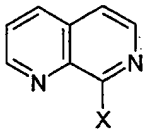
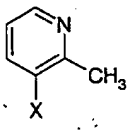
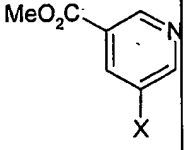
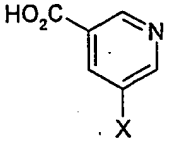
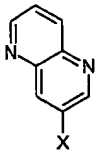
Example	R1	R2	R3	R4	R5
103	Et	H		Me	Ph
104	Et	H	3-Pyr	Me	4-Pyr
105	Et	H		Me	4-Pyr
106	Et	H		Me	4-Pyr
107	Et	H		Me	4-Pyr
108	Et	H		Me	3-Pyr
109	Et	H		Me	3-Pyr
110	Et	H		Me	3-Pyr

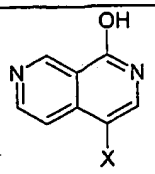
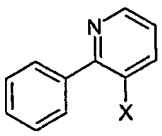
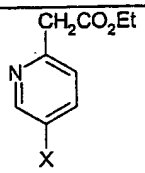
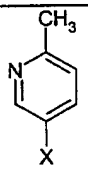
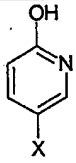
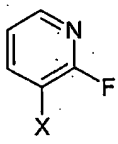
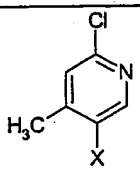
Example	R1	R2	R3	R4	R5
111	Et	H		Me	2-Thienyl
112	Et	H	3-Pyr	Me	2-Thienyl
113	Et	H	(4-CN)Ph	Me	2-Thienyl
114	Et	H		Me	2-Thienyl
115	Et	(4-CN)Ph	(4-CN)Ph	Me	2-Thienyl
116	C3H5CH2	H		Me	2-Thienyl
117	C3H5CH2	H	3-Pyr	Me	2-Thienyl
118	Et	H		Me	3-Thienyl

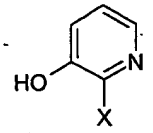
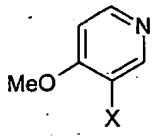
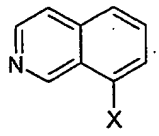
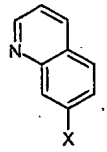
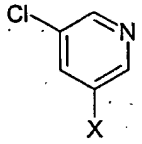
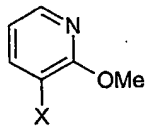
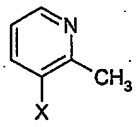
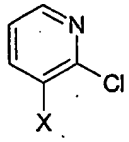
Example	R1	R2	R3	R4	R5
119	Et	H	(3-Cl)Ph	Me	3-Thienyl
120	Et	H	3-Pyr	Me	3-Thienyl
121	Et	H	(4-CN)Ph	Me	3-Thienyl
122	Et	H		Me	3-Thienyl
123	Et	H		Ph(CH2)2	Ph
124	Et	H	3-Pyr	Ph(CH2)2	Ph
125	Et	H		Ph(CH2)2	Ph
126	Et	H			Ph

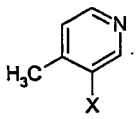
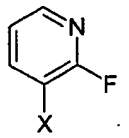
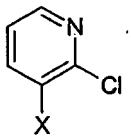
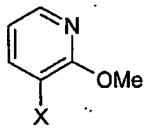
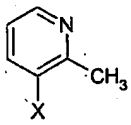
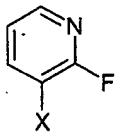
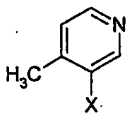
Example	R1	R2	R3	R4	R5
127	Et	H	3-Pyr		Ph
128	Et	H	(3-Cl)Ph	Me	
129	Et	H	(3-Cl)Ph	Me	
130	Et	H	(3-Cl)Ph	Me	
131	Et	H	3-Pyr	Me	3-Pyr
132	Et	H	(4-CO2H)Ph	Me	3-Pyr
133	Et	H		Me	Ph
134	Et	H		Me	4-Pyr

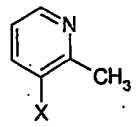
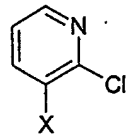
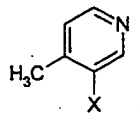
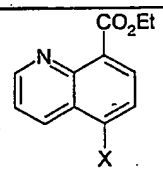
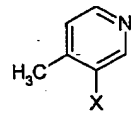
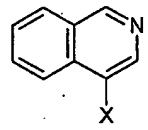
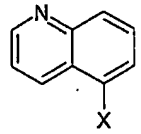
Example	R1	R2	R3	R4	R5
135	Et	H		Me	4-Pyr
136	Et	H		Me	Ph
137	Et	H		Me	Ph
138	Et	H		Me	Ph
139	Et	H		Me	Ph
140	Et	H		Me	Ph
141	Et	H		Me	Ph
142	Et	H		Me	Ph

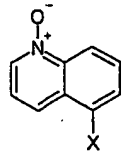
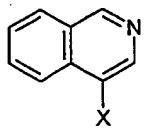
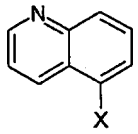
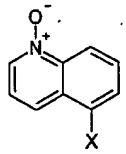
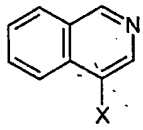
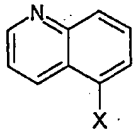
Example	R1	R2	R3	R4	R5
143	Et	H		Me	Ph
144	Et	H		Me	Ph
145	Et	H		Me	Ph
146	Et	H		Me	Ph
147	Et	H		CH2OH	Ph
148	Et	H		Me	Ph
149	Et	H		Me	Ph
150	Et	H		Me	Ph

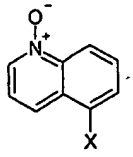
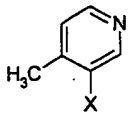
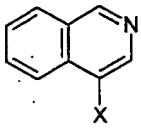
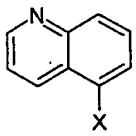
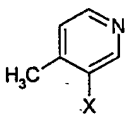
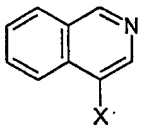
Example	R1	R2	R3	R4	R5
151	Et	H		Me	Ph
152	Et	H	2-Thienyl	Me	Ph
153	Et	H		Me	Ph
154	Et	H		Me	Ph
155	Et	H		Me	Ph
156	Et	H		Me	Ph
157	Et	H		Me	Ph
158	Et	H		Me	Ph

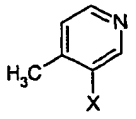
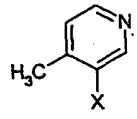
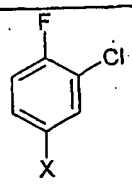
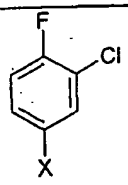
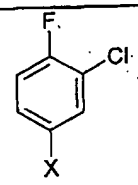
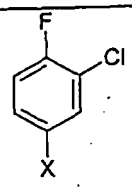
Example	R1	R2	R3	R4	R5
159	Et	H		Me	Ph
160	Et	H		Me	Ph
161	Et	H		Me	Ph
162	Et	H		Me	Ph
163	Et	H		Me	(3-F)Ph
164	Et	H		Me	(4-F)Ph
165	Et	H		Me	(4-F)Ph
166	Et	H		Me	(4-F)Ph

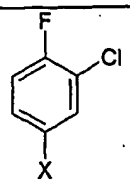
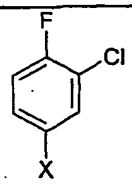
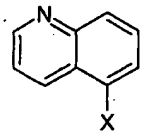
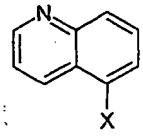
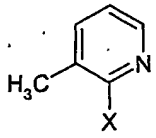
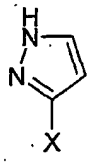
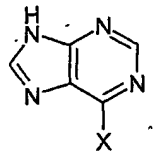
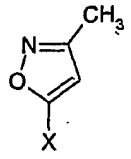
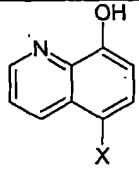
Example	R1	R2	R3	R4	R5
167	Et	H		Me	(4-F)Ph
168	Et	H		Me	(4-F)Ph
169	C3H5CH2	H		Me	(4-F)Ph
170	C3H5CH2	H		Me	(4-F)Ph
171	C3H5CH2	H		Me	(4-F)Ph
172	C3H5CH2	H		Me	(4-F)Ph
173	C3H5CH2	H		Me	(4-F)Ph
174	C3H5CH2	H	3-Pyr	Me	(4-F)Ph

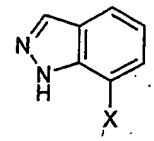
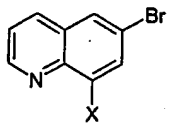
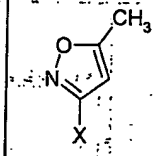
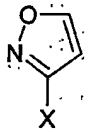
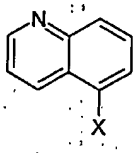
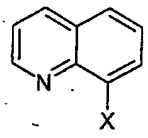
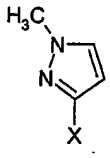
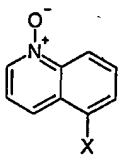
Example	R1	R2	R3	R4	R5
175	Et	H		Me	(3-Cl)Ph
176	Et	H		Me	(3-Cl)Ph
177	Et	H		Me	(3-Cl)Ph
178	Et	H		Me	Ph
179	Et	H		Me	Ph
180	Et	H		Me	(4-MeO)Ph
181	Et	H	3-Pyr	Me	(4-MeO)Ph
182	Et	H		Me	(4-MeO)Ph

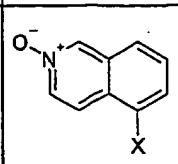
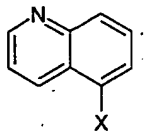
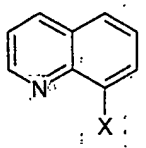
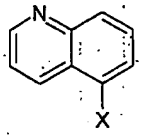
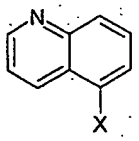
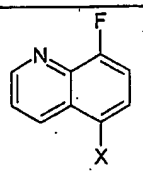
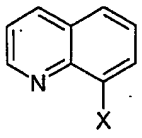
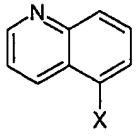
Example	R1	R2	R3	R4	R5
183	Et	H		Me	(4-MeO)Ph
184	Et	H		Me	(3-MeO)Ph
185	Et	H	3-Pyr	Me	(3-MeO)Ph
186	Et	H		Me	(3-MeO)Ph
187	Et	H		Me	(3-MeO)Ph
188	Et	H		Me	(4-Me)Ph
189	Et	H	3-Pyr	Me	(4-Me)Ph
190	Et	H		Me	(4-Me)Ph

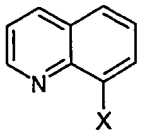
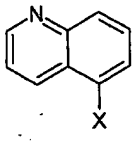
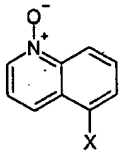
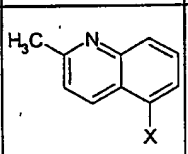
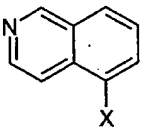
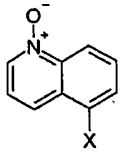
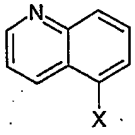
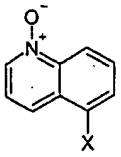
Example	R1	R2	R3	R4	R5
191	Et	H		Me	(4-Me)Ph
192	Et	H		Me	(4-Me)Ph
193	Et	H		Me	(3-Me)PH
194	Et	H	3-Pyr	Me	(3-Me)PH
195	Et	H		Me	(3-Me)PH
196	Et	H		Me	(3-Me)PH
197	Et	H		Me	(4-CO2Me)Ph
198	Et	H	3-Pyr	Me	(4-CO2Me)Ph

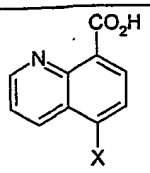
Example	R1	R2	R3	R4	R5
199	Et	H	3-Pyr	Me	(4-CO2H)Ph
200	Et	H		Me	(4-CO2Me)Ph
201	Et	H		Me	(4-CO2H)Ph
202	Et	H	3-Pyr	Me	(3-CO2Me)Ph
203	Et	H	3-Pyr	Me	(3-CO2H)Ph
204	Et	H		Me	4-Pyr
205	Et			Me	4-Pyr
206	Et	H		Me	3-Pyr

Example	R1	R2	R3	R4	R5
207	Et			Me	3-Pyr
208	CH2CO2Me	H		Me	Ph
209	CH2CO2H	H		Me	Ph
210	Et	H		Me	Ph
211	Et	H		Me	Ph
212	Et	H		Me	Ph
213	Et	H		Me	Ph
214	Et	H		Me	Ph

Example	R1	R2	R3	R4	R5
215	Et	H		Me	Ph
216	Et	H		Me	Ph
217	Et	H		Me	Ph
218	Et	H		Me	Ph
219	C3H5CH2	H		Me	Ph
220	C3H5CH2	H		Me	Ph
221	Et	H		Me	Ph
222	Et	H		Me	Ph

Example	R1	R2	R3	R4	R5
223	Et	H		Me	Ph
224	Et	H		Me	(3-Cl)Ph
225	Et	H		Me	(3-Cl)Ph
226	Et	H		Me	4-Pyr
227	Et	H		Me	3-Pyr
228	Et	H		Me	Ph
229	C3H5CH2	H		Me	(4-F)Ph
230	Et	H		Me	(4-F)Ph

Example	R1	R2	R3	R4	R5
231	Et	H		Me	(4-F)Ph
232	C3H5CH2	H		Me	(4-F)Ph
233	Et	H		Me	(3-Cl)Ph
234	Et	H		Me	Ph
235	Et	H		Me	(3-Cl)Ph
236	Et	H		Me	(4-F)Ph
237	Et	H		Me	(3-F)Ph
238	Et	H		Me	(3-F)Ph

Example	R1	R2	R3	R4	R5
239	Et	H		Me	Ph

EXAMPLE 1 (Scheme 1)

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

A mixture of the title compound of Preparation 14 (520 mg, 2.0 mmol), 3-fluorophenylboronic acid (560 mg, 4.0 mmol), anhydrous cupric acetate (540 mg, 3.0 mmol), triethylamine (0.56 mL, 4.0 mmol) and activated molecular sieves (1.6 g, 4 Å) in dry dichloromethane (25 mL) was stirred under air exposure at room temperature for 48 h. The reaction was filtered and the solvent removed under reduced pressure. The resulting residue was recrystallized from ethyl acetate (202 mg, 30% yield).

m.p. 196.6-197.7°C.

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.82 (s, 3H), 4.32 (q, 2H), 6.83 (m, 3H), 7.31 (m, 1H), 7.49 (bs,1H), 7.87 (d, 1H), 8.15 (s,1H), 8.68 (bs, 2H).

EXAMPLE 2 (Scheme 1)

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

Obtained as a solid (27%) from the title compound of Preparation 14 and 3-chlorophenylboronic acid following the procedure of Example 1.

m.p. 180.2-180.8°C.

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.80 (s, 3H), 4.31 (q, 2H), 6.98 (d, 1H), 7.08 (m, 1H), 7.18 (m,1H), 7.25 (m, 1H), 7.41 (bs, 1H), 7.78 (d, 1H), 8.17 (s,1H), 8.67 (bs, 2H).

EXAMPLE 3 (Scheme 1)

5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

Obtained as a solid (30%) from the title compound of Preparation 14 and 3,5-dichlorophenylboronic acid following the procedure of Example 1.

m.p. 219.9-220.4°C.

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.88 (s, 3H), 4.31 (q, 2H), 6.98 (s, 2H), 7.18 (s, 1H), 7.18 (m,1H), 7.60 (bs, 1H), 8.03 (m, 1H), 8.17 (s,1H), 8.72 (bs, 2H).

EXAMPLES 4-9 (Scheme 1)

4. **5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-pyridin-3-ylpyridazin-3(2H)-one**
5. **Methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzoate**
6. **5-Acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one**
7. **5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one**
8. **5-Acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-3-ylpyridazin-3(2H)-one**
9. **3-[(5-Acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile**

The title compounds were synthesized from the title compound of Preparation 14 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 2.

Table 2

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
4	385	8.1
5	393	7.2
6	353	7.1
7	369	7.7
8	365	5.7
9	360	6.8

EXAMPLES 10-14 (Scheme 1)

10. 5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

11. 5-Acetyl-2-(cyclopropylmethyl)-4-[(3,5-dichlorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

12. 5-Acetyl-2-(cyclopropylmethyl)-4-[(2-fluorophenyl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

13. 5-Acetyl-4-[(2-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

14. 3-{[5-Acetyl-2-(cyclopropylmethyl)-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

The title compounds were synthesized from the title compound of Preparation 17 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 3.

Table 3

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
10	395	8.6
11	430	9.4
12	379	7.9
13	395	8.5
14	386	7.6

EXAMPLE 15-18 (Scheme 1)

15. Methyl 4-{[5-acetyl-2-(2-hydroxyethyl)-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl]amino}benzoate

16. 5-Acetyl-4-[(2-fluorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

17. 5-Acetyl-4-[(2-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

18. 5-Acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 20 and 4-methoxycarbonylphenyl boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 4.

Table 4

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
15	408	6.1
16	368	5.9
17	384	6.5
18	384	6.9

EXAMPLE 19 (Scheme 1)

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-2-ylpyridazin-3(2H)-one

Obtained as a solid (27%) from the title compound of Preparation 15 and 3-chlorophenylboronic acid following the procedure of Example 1.

LRMS: m/z 369 $(M+1)^+$.

$\delta(CDCl_3)$: 1.42 (t, 3H), 2.01 (s, 3H), 4.38 (q, 2H), 6.90 (m, 1H), 7.20 (m, 4H), 7.82 (m,3H), 8.42 (d, 1H).

EXAMPLE 20 (Scheme 1)

3-[(5-Acetyl-2-ethyl-3-oxo-6-pyridin-2-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

Obtained as a solid (53%) from the title compound of Preparation 15 and 3-cyanophenylboronic acid following the procedure of Example 1.

$\delta(DMSO\text{-}d_3)$: 1.37 (t, 3H), 2.09 (s, 3H), 4.22 (q, 2H), 7.42 (m, 5H), 7.92 (m, 2H), 8.49 (m, 1H), 8.89 (s, 1H).

EXAMPLE 21 (Scheme 1)

5-Acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-2-ylpyridazin-3(2H)-one

Obtained as a solid (13%) from the title compound of Preparation 15 and 4-hydroxymethylphenylboronic acid following the procedure of Example 1.

LRMS: m/Z 364 $(M+1)^+$.

Retention Time: 4.9 min.

EXAMPLE 22 (Scheme 1)

3-{[5-Acetyl-2-(cyclopropylmethyl)-3-oxo-6-pyridin-2-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

Obtained as a solid (40%) from the title compound of Preparation 18 and 3-cyanophenylboronic acid following the procedure of Example 1.

m.p. 168.1-169.6°C.

$\delta(CD_3OD)$: 0.49 (m, 2H), 0.59 (m, 2H), 1.36 (m, 1H), 2.11 (s, 3H), 4.13 (d, 2H), 7.38 (m, 5H), 7.92 (m, 32H), 8.44 (m, 1H).

EXAMPLE 23-25 (Scheme 1)

23. **5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-2-ylpyridazin-3(2H)-one**
24. **5-Acetyl-2-(cyclopropylmethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-2-ylpyridazin-3(2H)-one**
25. **5-Acetyl-2-(cyclopropylmethyl)-4-[(3,5-dichlorophenyl)amino]-6-pyridin-2-ylpyridazin-3(2H)-one**

The title compounds were synthesized from the title compound of Preparation 18 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 5.

Table 5

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
23	394	8.5
24	390	8.9
25	429	9.7

EXAMPLE 26 (Scheme 1)

3-{[5-Acetyl-2-(2-hydroxyethyl)-3-oxo-6-pyridin-2-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

Obtained as a solid (26%) from the title compound of Preparation 21 and 3-cyanophenylboronic acid following the procedure of Example 1.

m.p. 194.3-195.0°C.

$\delta(CD_3OD)$: 2.10 (s, 3H), 4.01 (t, 2H), 4.40 (t, 2H), 6.90 (m, 1H), 7.35 (m, 6H), 7.92 (m, 2H), 8.46 (d, 1H).

EXAMPLE 27 (Scheme 1)

5-Acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

Obtained as a solid (22%) from the title compound of Preparation 21 and 3-chlorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 385 $(M+1)^+$.

Retention Time: 6.0 min.

EXAMPLES 28-29 (Scheme 1)

28. 5-Acetyl-4-[(3,5-dichlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

29. 5-Acetyl-2-(2-hydroxyethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-2-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 21 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 6.

Table 6

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
28	420	7.2
29	381	4.0

EXAMPLE 30 (Scheme 1)

5-Acetyl-2-ethyl-4-[(3-fluorophenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (15%) from the title compound of Preparation 16 and 3-fluorophenylboronic acid following the procedure of Example 1.

m.p. 195.1-195.9°C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.87 (s, 3H), 4.18 (q, 2H), 6.88 (m, 3H), 7.28 (m, 1H), 7.31 (d, 2H), 8.58 (d, 2H), 9.24 (s, 1H).

EXAMPLE 31 (Scheme 1)

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (68%) from the title compound of Preparation 16 and 3-chlorophenylboronic acid following the procedure of Example 1.

m.p. 176.4-177.0°C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.87 (s, 3H), 4.18 (q, 2H), 7.01 (m, 3H), 7.29 (m, 3H), 8.60 (m, 2H), 9.24 (s, 1H).

EXAMPLE 32 (Scheme 1)

5-Acetyl-2-ethyl-4-(1-naphthylamino)-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (53%) from the title compound of Preparation 16 and naphthalene-1-boronic acid following the procedure of Example 1.

m.p. 177.6-179.3°C.

δ(DMSO-d_6, 75°C): 1.37 (m, 6H), 4.23 (q, 2H), 7.23 (m, 3H), 7.37 (m, 1H), 7.54 (m, 2H), 7.70 (m, 1H), 7.92 (m, 1H), 8.01 (m, 1H), 8.55 (m, 2H), 8.89 (s,1H).

EXAMPLE 33 (Scheme 1)

5-Acetyl-2-ethyl-4-[(2-methylphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (17%) from the title compound of Preparation 16 and 2-methylphenylboronic acid following the procedure of Example 1.

m.p. 187.8-189.4°C.

δ(CD_3OD): 1.42 (t, 3H), 1.60 (s, 3H), 2.29 (s, 3H), 4.30 (q, 2H), 7.02 (m, 1H), 7.14 (m, 2H), 7.25 (m, 1H), 7.40 (m, 2H), 8.54 (m, 2H).

EXAMPLES 34-40 (Scheme 1)

34. Methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzoate

35. 5-Acetyl-2-ethyl-4-[(2-methoxyphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

36. 5-Acetyl-2-ethyl-4-[(3-methoxyphenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

37. 5-Acetyl-2-ethyl-4-[(2-fluorophenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

38. 5-Acetyl-4-[(2-chlorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

39. 3-[(5-Acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino] benzonitrile

40. 5-Acetyl-2-ethyl-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-4-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 16 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 7.

Table 7

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
34	392	7.0
35	364	6.9
36	364	6.9
37	352	6.8
38	368	7.5
39	359	6.4
40	364	5.4

EXAMPLE 41 (Hydrolisis: No scheme)

4-[(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

To a stirred solution of the title product of example 34 (0.38 g, 0.97 mmol) in 40 mL of a 3:2 MeOH/THF mixture a solution of lithium hydroxide (0.25 g, 5.88 mmol) in 4 mL of water was added and the mixture was stirred at room temperature overnight. It was acidified with HCl 2N until pH 6 and it was extracted with dichloromethane and washed with water and brine. It was dried on Na2SO4 and solvent removed to yield a crude product that was purified by column chromatography on SiO2 using CH2Cl2/MeOH as eluent. The title product was obtained in a 16% yield.

m.p. 251.6-252.6°C.

δ(DMSO-d_6): 1.34 (m, 3H), 1.93 (s, 3H), 4.20 (q, 2H), 7.08 (d, 2H), 7.33 (d, 2H), 7.79 (d, 2H), 8.60 (d, 2H), 9.38 (s,1H).

EXAMPLES 42-46 (Scheme 1)

42. 5-Acetyl-2-(cyclopropylmethyl)-4-[(2-fluorophenyl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

43. 5-Acetyl-4-[(2-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

44. 3-{[5-Acetyl-2-(cyclopropylmethyl)-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

45. 5-Acetyl-2-(cyclopropylmethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-4-ylpyridazin-3(2H)-one

46. 5-Acetyl-4-[(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 19 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 8.

Table 8

	ESI/MS m/e $(M+H)^+$	Retention Time (min)
42	378	7.8
43	394	8.5
44	385	7.4
45	390	6.4
46	394	8.4

EXAMPLES 47-51 (Scheme 1)

47. 5-Acetyl-4-[(2-fluorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

48. 5-Acetyl-4-[(2-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

49. 3-{[5-Acetyl-2-(2-hydroxyethyl)-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl]amino}benzonitrile

50. 5-Acetyl-2-(2-hydroxyethyl)-4-{[4-(hydroxymethyl)phenyl]amino}-6-pyridin-4-ylpyridazin-3(2H)-one

51. 5-Acetyl-4-[(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 22 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 9.

Table 9

	ESI/MS m/e $(M+H)^+$	Retention Time (min)
47	368	5.5
48	384	6.2
49	375	5.2
50	380	4.3
51	384	6.4

EXAMPLE 52 (Scheme 1)

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-thien-2-ylpyridazin-3(2H)-one

Obtained as a solid (20%) from the title compound of Preparation 26 and 3-chlorophenylboronic acid following the procedure of Example 1.

LRMS: m/Z 374 $(M+1)^+$.

$\delta(CDCl_3)$: 1.46 (t, 3H), 1.88 (s, 3H), 4.29 (q, 2H), 7.00 (m, 3H), 7.08 (m, 1H), 7.26 (m, 2H), 7.27 (m, 1H), 7.98 (m, 1H).

EXAMPLES 53-55 (Scheme 1)

53. 5-Acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

54. 5-Acetyl-4-[bis-(4-methoxycarbonylphenyl)-amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

55. 5-Acetyl-4-{bis[4-(hydroxymethyl)phenyl]amino}-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 14 and an excess of the corresponding arylboronic acid following the experimental procedure described in example 1. The ESI/MS data and HPLC retention times are summarized in Table 10.

Table 10

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
53	446	8.9
54	526	8.7
55	470	6.2

EXAMPLES 56-57 (Scheme 1)

56. 5-Acetyl-4-[bis(3-nitrophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

57. 5-acetyl-4-[bis(3-fluorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 16 and an excess of the corresponding arylboronic acid following the experimental procedure described in example 1. The ESI/MS data and HPLC retention times are summarized in Table 11.

Table 11

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
56	501	8.5
57	447	8.9

EXAMPLES 58-59 (Scheme 1)

58. 5-Acetyl-4-[bis(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

59. 5-Acetyl-4-[bis(3,5-dichlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-3-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 17 and an excess of the corresponding arylboronic acid following the experimental procedure

described in example 1. The ESI/MS data and HPLC retention times are summarized in Table 12.

Table 12

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
58	505	10.2
59	574	11.0

EXAMPLE 60 (Scheme 1)

5-Acetyl-4-[bis(4-methoxycarbonylphenyl)amino]-2-(2-hydroxyethyl)-6- pyridin-3-ylpyridazin-3(2H)-one

The title compound was synthesized from the title compound of Preparation 20 and an excess of 4-methoxycarbonylphenylboronic acid following the experimental procedure described in example 1.

LRMS: m/Z 542 $(M+1)^+$.

Retention Time: 8.0 min.

EXAMPLE 61 (Scheme 1)

5-Acetyl-4-[bis(3-chlorophenyl)amino]-2-(2-hydroxyethyl)-6-pyridin-2-ylpyridazin-3(2H)-one

The title compound was synthesized from the title compound of Preparation 21 and an excess of 3-chlorophenylboronic acid following the experimental procedure described in example 1.

LRMS: m/Z 495 $(M+1)^+$.

Retention Time: 9.6 min.

EXAMPLE 62 (Scheme 1)

5-Acetyl-4-[bis(3-chlorophenyl)amino]-2-(cyclopropylmethyl)-6-pyridin-4-ylpyridazin-3(2H)-one

The title compound was synthesized from the title compound of Preparation 19 and an excess of 3-chlorophenylboronic acid following the experimental procedure described in example 1.

LRMS: m/Z 505 $(M+1)^+$.

Retention Time: 10.2 min.

EXAMPLE 63 (Scheme 2)

5-Acetyl-2-ethyl-6-phenyl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

To a stirred solution of 200 mg (0.7 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (10 mL), 3-aminopyridine (0.098 mg, 1.04 mmol) was added portionwise. The resulting mixture was stirred at room temperature for five hours. The solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane/methanol 97:3) to yield the title compound (60 mg, 26% yield).

m.p. 185.6-186.3 °C.

δ(DMSO-d_6): 1.34 (m, 3H), 1.72 (s, 3H), 4.18 (q, 2H), 7.29 (m, 3H), 7.41 (m, 4H) 8.26 (d, 1H), 8.33 (d, 1H), 9.10 (s, 1H).

EXAMPLE 64 (Scheme 2)

5-Acetyl-4-[(3,5-dichloropyridin-4-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

To a stirred suspension of 50 mg (1.25 mmol) of sodium hydride in 5 ml of THF , 100 mg (0.62 mmol) of 4-amino-3,5-dichloropyridine in 5 ml of THF was added. The mixture was allowed stirring 30 minutes at room temperature and then cooled to 0°C. 150 mg (0.52 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 10 ml of THF was added. The reaction was allowed to warm to room temperature and to continue stirring for 12 hours. The mixture was acidified with 2N HCl to pH 2. Ethyl acetate was added and the organic layer was

washed with water, brine, dried over Na_2SO_4 anhydride and evaporated. The residue obtained (210 mg) was purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to yield the title compound (35 mg, 16.7 % yield).

m.p. 195.5-197.1 °C.

δ($CDCl_3$): 1.40 (m, 3H), 1.85 (s, 3H), 4.10 (q, 2H), 7.45 (bs, 5H), 8.40 (s, 2H), 8.80 (s, 1H).

EXAMPLE 65 (Scheme 2)

5-Acetyl-2-ethyl-6-phenyl-4-(pyrazin-2-ylamino)pyridazin-3(2H)-one

To a stirred solution of 75 mg (0.261 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 37 mg (0.392 mmol) of aminopyrazine was added. The resulting mixture was stirred at room temperature during 3 days and the final product was collected by filtration and washed with diethylether to yield the title compound (12 mg, 13.6 % yield).

m.p. 228.9-229.7°C.

δ(DMSO-d_6): 1.34 (m, 3H), 1.84 (s, 3H), 4.21 (q, 2H), 7.34 (m, 2H), 7.48 (m, 3H) 8.12 (m, 2H), 8.67 (s, 1H), 9.93 (s, 1H).

EXAMPLE 66 (Scheme 2)

5-Acetyl-2-ethyl-6-phenyl-4-(pyrimidin-2-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.348 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 5 ml of ethanol, 430 mg (4.524 mmol) of 2-aminopyrimidine was added. The resulting mixture was stirred at 50°C during five days and the final product was collected by filtration and washed with diethylether to yield the title compound (42 mg, 35.6 % yield).

m.p. 197.1-198.3 °C.

δ(DMSO-d_6): 1.33 (m, 3H), 1.96 (s, 3H), 4.19 (q, 2H), 7.02 (m, 1H), 7.37 (m, 2H) 7.49 (m, 3H), 8.52 (m, 2H), 9.02 (s, 1H).

EXAMPLE 67 (Scheme 2)

5-Acetyl-2-ethyl-6-phenyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.348 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 5 ml of ethanol, 75 mg (0.522 mmol) of 8-aminoquinoline was added. The resulting mixture was stirred at room temperature for two hours and the final product was collected by filtration and washed with diethylether to yield the title compound (100 mg, 74.6 % yield).

m.p. 179.2.1-180.3°C.

δ($CDCl_3$): 1.49 (m, 3H), 1.75 (s, 3H), 4.34 (q, 2H), 7.25 (m, 1H), 7.45 (m, 7H) 7.56 (m, 1H), 8.17 (dd, 1H), 8.92 (d, 1H), 9.55 (s, 1H).

EXAMPLE 68 (Scheme 2)

5-Acetyl-2-ethyl-4-[(5-nitropyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

To a solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 77 mg (0.556 mmol) of 2-amino-5-nitropyridine was added. The resulting mixture was irradiated in microwave oven for seven hours at 120°C. The final product was collected by filtration and washed with diethylether to yield the title compound (36 mg, 34.3 % yield).

m.p. 200.3-201.1°C.

δ(DMSO-d_6): 1.35 (m, 3H), 1.92 (s, 3H), 4.22 (q, 2H), 7.39 (m, 3H), 7.49 (m, 3H), 8.41-8.45 (dd, 1H), 8.92 (d, 1H), 10.34 (s, 1H).

EXAMPLE 69 (Scheme 2)

5-Acetyl-2-ethyl-4-(1H-indol-4-ylamino)-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 55 mg (0.417 mmol) of 4-aminoindole was added. The resulting mixture was

stirred at room temperature for one hour and the final product was collected by filtration and washed with diethylether to yield the title compound (83 mg, 79.8 % yield).

m.p. 223.2-224.9°C.

$\delta(CDCl_3)$: 1.27 (s, 3H), 1.36 (m, 3H), 4.19 (q, 2H), 6.33 (s, 1H), 6.66-6.67 (d, 1H) 6.95 (m, 1H), 7.25 (m, 3H), 7.31-7.37 (m, 4H), 8.76 (s, 1H), 11.20 (s, 1H).

EXAMPLES 70-78 (Scheme 2)

70. 5-Acetyl-4-(1,3-benzothiazol-6-ylamino)-2-ethyl-6-phenylpyridazin-3(2H)-one

71. 5-Acetyl-2-ethyl-6-phenyl-4-(thianthren-1-ylamino)pyridazin-3(2H)-one

72. Methyl 3-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]thiophene-2-carboxylate

73. 5-Acetyl-2-ethyl-4-[(4-methylpyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

74. 5-Acetyl-2-ethyl-6-phenyl-4-(1H-1,2,4-triazol-5-ylamino)pyridazin-3(2H)-one

75. 5-Acetyl-2-ethyl-4-[(6-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

76. 5-Acetyl-2-ethyl-4-(2H-indazol-5-ylamino)-6-phenylpyridazin-3(2H)-one

77. Methyl 4-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]thiophene-3-carboxylate

78. 5-Acetyl-2-ethyl-6-phenyl-4-(pyridin-2-ylamino)pyridazin-3(2H)-one

The title compounds were synthesized from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) and the corresponding aniline or aminopyridine following the procedure of Example 67. The ESI/MS data and HPLC retention times are summarized in Table 13.

Table 13

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
70	390	8.2
71	471	10.5
72	397	9.1
73	348	5.0
74	324	7.5

75	364	8.3
76	373	7.7
77	398	8.8
78	335	4.8

EXAMPLE 79 (Hydrolisis: No scheme)

3-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]thiophene-2-carboxylic acid

The title compound was synthesized from the title compound of example 72 following the experimental procedure described in example 41.

LRMS: m/Z 383 $(M+1)^+$.

Retention Time: 8.5 min.

EXAMPLE 80 (Scheme 2)

5-Acetyl-2-ethyl-4-[(3-methylcinnolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 66 mg (0.417 mmol) of 3-methylcinnolin-5-amine was added. The resulting mixture was stirred at room temperature for one day. The final product was collected by filtration and purified by column chromatography (silica gel, ethyl acetate/hexane 2:1) to yield the title compound (65 mg, 58.6% yield).

m.p. 235.4-237.7°C.

δ(DMSO-d_6): 1.37 (m, 3H), 1.41 (s, 3H), 2.91 (s, 3H), 4.22 (q, 2H), 7.25 (m, 2H) 7.35-7.40 (m, 3H), 7.53 (d, 1H), 7.67-7.72 (t, 1H), 8.10 (s, 1H), 8.24 (d, 1H), 9.19 (s, 1H).

EXAMPLE 81 (Scheme 2)

5-Acetyl-2-ethyl-4-[(2-methylquinolin-8-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 66 mg (0.417 mmol) of 2-methylquinolin-8-amine was added. The resulting mixture was stirred at room temperature for one hour and the final product was collected by filtration and washed with diethylether to yield the title compound (97 mg, 93.3 % yield).

m.p. 172.2-172.6°C.

δ(DMSO-d_6): 1.22 (m, 3H), 1.52 (s, 3H), 2.54 (s, 3H), 4.07 (q, 2H), 7.02 (d, 1H), 7.21-7.30 (m, 6H), 7.35 (d, 1H), 7.46 (d, 1H), 8.13 (d, 1H), 9.15 (s, 1H).

EXAMPLE 82 (Scheme 2)

5-Acetyl-2-ethyl-6-phenyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 60 mg (0.417 mmol) of 5-aminoquinoline was added. The resulting mixture was stirred at room temperature for four hours and the final product was collected by filtration and washed with diethylether to yield the title compound (80 mg, 74.8 % yield).

m.p. 219.9-221.1°C.

δ(DMSO-d_6): 1.31 (s, 3H), 1.38 (m, 3H), 4.22 (q, 2H), 7.24 (m, 2H) 7.34-7.38 (m, 4H), 7.55-7.63 (m, 2H), 7.86 (d, 1H), 8.42 (d, 1H), 8.92 (d, 1H), 9.19 (s, 1H).

EXAMPLE 83 (Scheme 2)

5-Acetyl-2-ethyl-4-(1H-indol-5-ylamino)-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 55 mg (0.417 mmol) of 5-aminoindole was added. The resulting mixture was stirred at room temperature for one hour and the final product was collected by filtration and washed with diethylether to yield the title compound (97 mg, 93.3 % yield).

m.p. 242.6-243.1°C.

δ(DMSO-d_6): 1.34 (m, 3H), 1.47 (s, 3H), 4.17 (q, 2H), 6.33 (bs, 1H), 6.83 (d,1H), 7.24-7.37 (m, 8H), 8.77 (s, 1H), 11.09 (s, 1H).

EXAMPLE 84 (Scheme 2)

5-Acetyl-2-ethyl-4-(isoquinolin-5-ylamino)-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 60 mg (0.417 mmol) of 5-isoquinolinamine was added. The resulting mixture was stirred at room temperature for three days. The final product was collected by filtration and purified by column chromatography (silica gel, ethyl acetate/hexane 7:3) to yield the title compound (20 mg, 12.4% yield).

δ(DMSO-d_6): 1.31 (s, 3H), 1.38 (m, 3H), 4.22 (q, 2H), 7.24 (m, 2H) 7.38 (m, 3H), 7.53 (m, 2H), 7.85 (d, 1H), 7.97 (d, 1H), 8.53 (d, 1H), 9.18 (s, 1H), 9.32 (s, 1H).

EXAMPLE 85 (Scheme 2)

5-Acetyl-2-ethyl-4-[(6-methoxyquinolin-8-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in 4 ml of ethanol, 73 mg (0.417 mmol) of 8-amino-6-methoxyquinoline was added. The resulting mixture was stirred at room temperature for two hours and the final product was collected by filtration and washed with diethylether to yield the title compound (88 mg, 76.5 % yield).

m.p. 183.1-184.0°C.

δ(DMSO-d_6): 1.34 (m, 3H), 1.68 (s, 3H), 3.84 (s, 3H), 4.21 (q, 2H), 6.81 (s, 1H), 7.08 (s, 1H), 7.36-7.46 (m, 5H), 7.53-7.57 (m, 1H), 8.27 (d, 1H), 8.73 (d, 1H), 9.31 (s, 1H).

EXAMPLE 86 (Scheme 2)

5-Acetyl-4-[(5-bromoquinolin-8-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

To a stirred solution of 40 mg (0.139 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 8-amino-5-bromoquinoline (47 mg, 0.209 mmol) was added. The resulting mixture was stirred at room temperature for five days and heated at 50 °C during four days. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 4:1) to yield the title compound (16 mg, 25% yield).

m.p. 148.1-149.0°C.

δ(DMSO-d_6): 1.35 (m, 3H), 1.70 (s, 3H), 4.20 (q, 2H), 7.13 (d, 1H), 7.39-7.46 (m, 5H) 7.76 (m, 1H), 7.84 (d, 1H), 8.50 (d, 1H), 8.99 (d, 1H), 9.41 (s, 1H).

EXAMPLE 87 (Scheme 2)

5-Acetyl-2-ethyl-4-[(4-methylpyrimidin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 2-amino-4-methylpyrimidine (46 mg, 0.417 mmol) was added. The resulting mixture was stirred at 50 °C during five days. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 2:1) to yield the title compound (11 mg, 11.3% yield).

LRMS: m/Z 350 $(M+1)^+$.

Retention Time: 7.4 min.

EXAMPLE 88 (Scheme 2)

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-(pyridin-3-ylamino)- pyridazin-3(2H)-one

Obtained from 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) and pyridin-3-ylamine following the procedure of Example 67. The product was purified by preparative HPLC/MS.

LRMS: m/Z 369 $(M+1)^+$.

Retention Time: 8.2 min.

EXAMPLE 89 (Scheme 2)

5-Acetyl-6-(3-chlorophenyl)-2-cyclopropylmethyl-4-(pyridin-3-ylamino)-pyridazin-3(2H)-one

Obtained from the title compound of preparation 40 and pyridin-3-ylamine following the procedure of Example 67. The product was purified by preparative HPLC/MS.

LRMS: m/Z 395 $(M+1)^+$.

Retention Time: 9.1 min.

EXAMPLE 90 (Scheme 2)

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-(pyridin-3-ylamino)-pyridazin-3(2H)-one

Obtained from the title compound of preparation 36 and pyridin-3-ylamine following the procedure of Example 67. The product was purified by preparative HPLC/MS.

LRMS: m/Z 353$(M+1)^+$.

Retention Time: 7.4 min.

EXAMPLE 91 (Scheme 2)

5-Acetyl-6-(3-fluorophenyl)-2-isopropyl-4-(pyridin-3-ylamino)-pyridazin-3(2H)-one

Obtained from the title compound of preparation 38 and pyridin-3-ylamine following the procedure of Example 67. The product was purified by preparative HPLC/MS.

LRMS: m/Z 367 $(M+1)^+$.

Retention Time: 8.3 min.

EXAMPLE 92 (Scheme 2)

5-Acetyl-2-cyclopropylmethyl-6-(3-fluorophenyl)-4-(pyridin-3-ylamino)-pyridazin-3(2H)-one

Obtained from the title compound of preparation 37 and pyridin-3-ylamine following the procedure of Example 67. The product was purified by preparative HPLC/MS.

LRMS: m/Z 379 $(M+1)^+$.

Retention Time: 8.4 min.

EXAMPLE 93 (Scheme 2)

5-Acetyl-6-(4-fluorophenyl)-2-ethyl-4-(pyridin-3-ylamino)-pyridazin-3(2H)-one

Obtained from the title compound of preparation 30 and pyridin-3-ylamine following the procedure of Example 67. The product was purified by preparative HPLC/MS.

LRMS: m/Z 353 $(M+1)^+$.

Retention Time: 7.4 min.

EXAMPLE 94

5-Acetyl-6-(1H-benzoimidazol-2-yl)-4-(3-chloro-phenylamino)-2-ethyl-2H-pyridazin-3-one

To 10 mL of dry toluene under nitrogen, trimethylalumminium (1.05 mL of a 2M solution in toluene) was added and the solution was cooled down to 0ºC. Then 1,2-diaminobenzene (68 mg, 0.63 mmol) was added in portions and the mixture was stirred at 0ºC for 30 min and at 15ºC for 1 hour. Then, the title product of preparation 45 (150 mg, 0.42 mmol) was added in one portion and the final mixture was refluxed for 1.5 hours. Then it was let to warm to room temperature and water and methanol were carefully added. The white precipitate thus formed was filtered and the mother liquor

was neutralized with HCl 2N and solvent was removed. Finally the residue was partiotioned between water and dichloromethane and the organic layer was washed with brine. Dried and solvent removed to yield a crude product that was purified by column chromatography.

LRMS: m/Z 408 $(M+1)^+$.

Retention Time: 8.0 min.

$\delta(CDCl_3)$: 1.41 (t, 3H), 2.01 (s, 3H), 4.38 (q, 2H), 6.85 (m, 2H), 7.10 (m, 5H), 7.38 (s, 1H), 7.78 (s, 1H)

EXAMPLES 95-96 (Scheme 1)

95. 5-Acetyl-6-benzooxazol-2-yl-4-(3-chlorophenylamino)-2-ethyl-pyridazin-3(2H)-one

96. 5-Acetyl-6-benzooxazol-2-yl-4-(3-fluorophenylamino)-2-ethyl-pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 48 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 14.

Table 14

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
95	408	9.7
96	392	9.4

EXAMPLES 97-98 (Scheme 1)

97. 5-Acetyl-6-benzooxazol-2-yl-4-[bis-(3-chlorophenyl)-amino]-2-ethyl-pyridazin-3(2H)-one

98. 5-Acetyl-6-benzooxazol-2-yl-4-[bis-(3-fluorophenyl)-amino]-2-ethyl-pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 48 and an excess of the corresponding arylboronic acid following the experimental procedure

described in example 1. The ESI/MS data and HPLC retention times are summarized in Table 15.

Table 15

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
97	519	10.9
98	486	10.4

EXAMPLES 99-100

99. 5-Acetyl-6-(1,3-benzoxazol-2-yl)-2-ethyl-4-[(3-methoxyphenyl) amino]pyridazin-3(2H)-one

100. 5-Acetyl-6-(1,3-benzoxazol-2-yl)-2-ethyl-4-{[4-(hydroxymethyl) phenyl]amino}pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 48 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 16.

Table 16

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
99	405	9.4
100	405	8.2

EXAMPLE 101

5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-phenylpyridazin-3(2H)-one

A mixture of the title compound of Preparation 49 (2.2 g, 8.56 mmol), 4-bromoisoquinoline (2.14 g, 10.3 mmol), anhydrous cuprous iodide (170 mg, 0.89 mmol) mmol), N,N'-dimethylethylenediamine (0.185 ml, 0.89 mmol) and potassium carbonate

(1.73 g, 12.5 mmol) in dry dioxane under argon was stirred in a sealed tube at 130°C for 24 h. The reaction was filtered and the solvent removed under reduced pressure. The resulting residue was purified by flash column cromathography (SiO_2, dichloromethane-ethyl acetate) to yield the title product (450 mg, 14% yield).

m.p. 215.9-216.5°C.

$\delta(CDCl_3)$: 1.43 (s, 3H), 1.48 (t, 3H), 4.34 (q, 2H), 7.35 (m, 5H), 7.70 (m, 1H), 7.79 (m, 1H), 8.08 (m, 2H), 8.29 (m, 2H), 9.16 (s, 1H).

EXAMPLES 102-103

102. 5-Acetyl-2-ethyl-4-(1,6-naphthyridin-8-ylamino)-6-phenylpyridazin-3(2H)-one

103. 5-Acetyl-2-ethyl-4-[(5-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 49 and the corresponding bromide following the procedure of Example 101. The ESI/MS data and HPLC retention times are summarized in Table 17.

Table 17

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
102	386	15*
103	365	7.9

EXAMPLE 104

5-Acetyl-2-ethyl-6-pyridin-4-yl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained as a yellow solid (69%) from the title compound of Preparation 16 and 3-bromopyridine following the procedure of Example 101.

LRMS: m/Z 336 $(M+1)^+$.

* Chromatografic method B.

Retention Time: 6 min.

δ($CDCl_3$): 1.45 (t, 3H), 1.79 (s, 3H), 4.30 (q, 2H), 7.30 (m, 3H), 7.41 (m, 1H), 8.42 (m, 3H), 8.68 (m, 2H).

EXAMPLE 105

5-Acetyl-2-ethyl-4-[(4-methylpyridin-3-yl)amino]-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (31%) from the title compound of Preparation 16 and 3-bromo-4-methylpyridine following the procedure of Example 101.

m.p. 207.8-208.9°C.

δ(DMSO-d_3): 1.33 (t, 3H), 1.68 (s, 3H), 2.21 (s, 3H), 4.16 (m, 2H), 7.22 (m, 1H), 7.27 (m, 2H), 8.17 (m, 2H), 8.57 (m, 2H), 8.82 (m, 1H).

EXAMPLES 106-107

106. 5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-pyridin-4-ylpyridazin-3(2H)-one

107. 5-Acetyl-2-ethyl-6-pyridin-4-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 16 and the corresponding bromide following the procedure of Example 101. The ESI/MS data and HPLC retention times are summarized in Table 18.

Table 18

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
106	386	6.4
107	388	7.9

EXAMPLE 108

5-Acetyl-2-ethyl-4-[(4-methylpyridin-3-yl)amino]-6-pyridin-3-ylpyridazin-3(2H)-one

Obtained as a solid (21%) from the title compound of Preparation 14 and 3-bromo-4-methylpyridine following the procedure of Example 101.

m.p. 194.7-195.4°C.

δ(DMSO-d_3): 1.35 (t, 3H), 1.52 (s, 3H), 2.22 (s, 3H), 4.20 (q, 2H), 7.24 (d, 1H), 7.40 (m, 1H), 7.68 (m, 1H), 8.25 (m, 2H), 8.48 (s, 1H), 8.58 (m, 1H), 8.87 (s, 1H).

EXAMPLES 109-110

109. 5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-pyridin-3-ylpyridazin-3(2H)-one

110. 5-Acetyl-2-ethyl-6-pyridin-3-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 14 and the corresponding bromide following the procedure of Example 101. The ESI/MS data and HPLC retention times are summarized in Table 19:

Table 19

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
109	386	6.6
110	389	15*

EXAMPLE 111

5-Acetyl-2-ethyl-4-(quinolin-5-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

Obtained as a solid (50%) from the title compound of Preparation 26 and quinoline-5-boronic acid following the procedure of Example 1.

m.p. 214.2-215.0°C.

* Chromatografic method B.

δ($CDCl_3$): 1.43 (t, 3H), 1.51 (s, 3H), 4.32 (q, 2H), 6.85 (m, 1H), 6.90 (m, 1H), 7.36 (m, 2H), 7.52 (m, 1H), 7.64 (m, 1H), 8.05 (m, 2H), 8.42 (m,1H), 9.00 (m, 1H).

EXAMPLES 112-114

112. 5-Acetyl-2-ethyl-4-(pyridin-3-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

113. 4-[(5-Acetyl-2-ethyl-3-oxo-6-thien-2-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

114. 5-Acetyl-2-ethyl-6-thien-2-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 26 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 20.

Table 20

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
112	341	12
113	365	8.9
114	394	10.2

EXAMPLE 115

5-Acetyl-4-(bis (4-cyanophenyl)amino)- 2-ethyl-6-thien-2-ylpyridazin-3(2H)-one

Obtained as a solid from the title compound of Preparation 26 and an excess of 4-cyanophenylboronic acid following the experimental procedure described in Example 1.

LRMS: m/Z 466 $(M+1)^+$.

Retention Time: 9.9 min.

EXAMPLES 116-117

116. 5-Acetyl-2-(cyclopropylmethyl)-4-(quinolin-5-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

117. 5-Acetyl-2-(cyclopropylmethyl)-4-(pyridin-3-ylamino)-6-thien-2-ylpyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 51 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 21.

Table 21

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
116	417	15*
117	367	14*

EXAMPLE 118

5-Acetyl-2-ethyl-4-(quinolin-5-ylamino)-6-thien-3-ylpyridazin-3(2H)-one

Obtained as a solid (52%) from the title compound of Preparation 55 and quinoline-5-boronic acid following the procedure of Example 1.

m.p. 186.6-187.3°C.

$\delta(CDCl_3)$: 1.45 (s, 3H), 1.51 (t, 3H), 4.34 (q, 2H), 7.11 (m, 1H), 7.30 (m, 3H), 7.52 (m, 1H), 7.65 (m, 1H), 8.08 (m, 2H), 8.43 (m,1H), 8.99 (m, 1H).

EXAMPLES 119-122

119. 5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-thien-3-ylpyridazin-3(2H)-one

120. 5-Acetyl-2-ethyl-4-(pyridin-3-ylamino)-6-thien-3-ylpyridazin-3(2H)-one

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* Chromatografic method B.

121. 4-[(5-Acetyl-2-ethyl-3-oxo-6-thien-3-yl-2,3-dihydropyridazin-4-yl)amino]benzonitrile

122. 5-Acetyl-2-ethyl-6-thien-3-yl-4-[(3,4,5-trifluorophenyl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 55 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 22.

Table 22

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
119	374	9.4
120	341	6.9
121	365	9.3
122	394	10.1

EXAMPLE 123

2-Ethyl-6-phenyl-5-(3-phenylpropanoyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

Obtained as a solid (50%) from the title compound of Preparation 58 and quinoline-5-boronic acid following the procedure of Example 1.

m.p. 164.0-165.8°C.

$\delta(CDCl_3)$: 1.48 (t, 3H), 1.79 (t, 2H), 2.01 (t, 2H), 4.35 (q, 2H), 6.42 (m, 2H), 7.05 (m, 3H), 7.32 (m, 6H), 7.51 (m, 1H), 7.64 (m, 1H), 8.09 (m, 2H), 8.46 (m,1H), 9.00 (m, 1H).

EXAMPLES 124-125

124. 2-Ethyl-6-phenyl-5-(3-phenylpropanoyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

125. 2-Ethyl-4-(isoquinolin-4-ylamino)-6-phenyl-5-(3-phenylpropanoyl)pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 58 and the corresponding bromide following the procedure of Example 101. The ESI/MS data and HPLC retention times are summarized in Table 23.

Table 23

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
124	425	17*
125	475	17*

EXAMPLES 126-127

126. 2-Ethyl-6-phenyl-4-(quinolin-5-ylamino)-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one

127. 2-Ethyl-6-phenyl-4-(pyridin-3-ylamino)-5-(3-thien-3-ylpropanoyl)pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 59 and the corresponding boronic acid following the procedure of Example 1. The ESI/MS data and HPLC retention times are summarized in Table 24.

Table 24

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
126	481	17*
127	431	16*

* Chromatografic method B.

EXAMPLE 128

5-Acetyl-4-[(3-chlorophenyl)amino]-2-ethyl-6-(1H-imidazo[4,5-b]pyridin-2-yl)pyridazin-3(2H)-one

Obtained as a solid (7%) from the title compound of Preparation 45 and 2,3-diaminopyridine acid following the experimental procedure described in example 94.

LRMS: m/Z 409 $(M+1)^+$.

Retention Time: 6.3 min.

EXAMPLE 129

5-Acetyl-6-(1,3-benzothiazol-2-yl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one

Obtained as a solid (22%) from the title compound of Preparation 45 and 2-aminobenzenethiol following the experimental procedure described in example 94.

LRMS: m/Z 425 $(M+1)^+$.

Retention Time: 10.5 min.

EXAMPLE 130

5-Acetyl-6-(1-benzofuran-2-yl)-4-[(3-chlorophenyl)amino]-2-ethylpyridazin-3(2H)-one

Obtained as a solid (31%) from the title compound of Preparation 63 and 3-chlorophenyl boronic acid following the procedure of Example 1.

LRMS: m/Z 408 $(M+1)^+$.

Retention Time: 10.2 min.

EXAMPLE 131

5-Acetyl-2-ethyl-6-pyridin-3-yl-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained as a solid from the title compound of Preparation 14 and 3-pyridineboronic acid following the procedure of Example 1.

LRMS: m/Z 334 $(M+1)^+$.

Retention Time: 4.9 min.

EXAMPLE 132

4-[(5-Acetyl-2-ethyl-3-oxo-6-pyridin-3-yl-2,3-dihydropyridazin-4-yl)amino]benzoic acid

Obtained as a solid from the title compound of Example 5 following the procedure of Example 41.

LRMS: m/Z 379 $(M+1)^+$.

Retention Time: 6.1 min.

EXAMPLE 133

5-Acetyl-2-ethyl-4-[(1-oxidopyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 50-55% *m*-chloroperbenzoic acid (130 mg, 0.38 mmol aprox.) in dichloromethane (2 ml), a solution of the title product of example 63 (126 mg, 0.38 mmol) in dichloromethane (2 ml) was added dropwise and the resulting mixture was stirred at rt overnight. Then it was diluted with dichloromethane and poured onto 10% sodium sulphite solution. The organic layer was further washed with saturated sodium bicarbonate solution and brine. It was then dried and solvent removed to yield a crude product that was purifiedd by preparative HPLC/MS.

LRMS: m/Z 351 $(M+1)^+$.

Retention Time: 6.9 min.

EXAMPLE 134

Ethyl 3-(5-acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-ylamino)benzoate

Obtained as a solid (67%) from the title compound of Preparation 16 and 3-ethoxycarbonylphenylboronic acid following the procedure of Example 1.

LRMS: m/Z 407 $(M+1)^+$.

$\delta(CDCl_3)$: 1.38 (t, 3H), 1.46 (t, 3H), 1.58 (s, 3H), 4.35 (m, 4H), 7.28 (m, 3H), 7.41 (m, 1H), 7.70 (s, 1H), 7.88 (m, 1H), 8.29 (s, 1H), 8.63 (m, 2H).

EXAMPLE 135

3-[(5-Acetyl-2-ethyl-3-oxo-6-pyridin-4-yl-2,3-dihydropyridazin-4-yl)amino] benzamide

To a 0ºC precooled solution of saturated ammonia in THF (2 ml) under argon, trimethylaluminium (0.307 mL, 0.615 mmol) was added and the mixture was stirred for 30 min. Then, a solution of the title compound of Example 134 (50 mg, 0.123 mmol) in dry THF (1 mL) was added dropwise and the final mixture was stirred at rt overnight. Some more trimethylalumminium (0.307 mL, 0.615 mmol) was added and the mixture was refluxed overnight. It was then let to cool down and water was added. The solid thus formed was removed by filtration and the mother liquor was diluted with water, neutralized with 0.1 M HCl and extracted with dichloromethane. The organic layer was washed with water and brine and dried. Finally, solvent was removed to yield a crude product that was purified by preparative HPLC/MS (20% yield).

LRMS: m/Z 78 $(M+1)^+$.

Retention Time: 5.1 min.

EXAMPLE 136

5-Acetyl-2-ethyl-6-phenyl-4-(thieno[2,3-b]pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained (27%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and thieno[2,3-b]pyridin-3-ylamine (Klemm, L.H.,

Zell, R., Barnish, I.T., Klemm, R.A., *J. Het. Chem*, 1970, 373-379) following the procedure of Example 67.

LRMS: m/Z 391 $(M+1)^+$

Retention Time: 14 min*.

EXAMPLE 137

5-Acetyl-2-ethyl-4-[(6-fluoropyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

Obtained (65%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, 40, 1417) and 6-fluoropyridin-3-ylamine (Rewcastle, G. W., Denny, W.A, Winters, R.T, *J. Chem Soc, Perkin Trans.* 1, 1996, 18, 2221-2226) following the procedure of Example 67.

m.p. 183.1-184.3°C

δ(CDCl3): 1.43 (t, 3H), 1.68 (s, 3H), 4.26 (q, 2H), 6.92 (dd,1H), 7.42 (m, 5H), 7.54 (m, 1H), 8.05 (d, 1H), 8.61 (s, 1H)

EXAMPLE 138

5-Acetyl-2-ethyl-4-[(2-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

Obtained (17%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 2-methylpyridin-3-ylamine (Nantka-Namirski, P., Kaczmarczyk, C., Toba, L., *Acta Poloniae Pharmaceutica*. 1967, 24(3), 231-237) following the procedure of Example 63. The product was purified by column cromatography (silica gel, hexane/ethyl acetate 1:1).

m.p. 167.9-168.6°C

δ(CDCl3): 1.42 (t, 3H), 1.64 (s, 3H), 2.60 (s, 3H), 4.27 (q, 2H), 7.18 (m,1H), 7.26 (m, 1H), 7.42 (m, 5H), 8.25 (s, 1H), 8.39 (m, 1H)

* Chromatografic method B.

EXAMPLE 139

5-Acetyl-4-{[2-(dimethylamino)pyridin-3-yl]amino}-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained (20%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 3-amino-2-dimethylaminopyridine following the procedure of Example 63. The product was purified by column cromatography (silica gel, hexane/ethyl acetate 5:1).

m.p. 135.1-137.0°C

δ(CDCl3): 1.42 (t, 3H), 1.64 (s, 3H), 2.93 (s, 6H), 4.31 (q, 2H), 6.88 (m,1H), 7.16 (m, 1H), 7.42 (m, 5H), 8.05 (m, 1H), 8.19 (m, 1H).

EXAMPLE 140

5-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]pyridine-2-carboxylic acid

Obtained (43%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 5-aminopyridine-2-carboxylic acid (De Waal, A., Hartog, A. F., De Jong, L., *Biochimica et Biophysica Acta*, 1988, 953(1), 20-25) following the procedure of Example 67.

m.p. 226.1-226.8°C

δ(DMSO-d6): 1.38 (m, 3H), 1.92 (s, 3H), 4.18 (q, 2H), 7.38 (m, 1H), 7.42 (m,5H), 7.86 (d, 1H), 8.42 (s, 1H), 9.38 (s, 1H), 12.92 (1H, s).

EXAMPLE 141

5-Acetyl-2-ethyl-4-[(2-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

Obtained (43%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 2-methoxypyridin-3-ylamine (Hwu, J.R., Wong, F.F., Shiao, M.J., *J. Org. Chem,* 1992, 57(19), 5254-5255) following the procedure of Example 67.

m.p. 170.2-170.5°C

δ(CDCl3): 1.42 (t, 3H), 1.68 (s, 3H), 3.98 (s, 3H), 4.29 (q, 2H), 6.86 (m,1H), 7.26 (m, 1H), 7.39 (m, 5H), 7.98 (m, 1H), 8.32 (s, 1H)

EXAMPLE 142

5-Acetyl-2-ethyl-4-(1H-indazol-4-ylamino)-6-phenylpyridazin-3(2H)-one

Obtained (83%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 1H-indazol-4-ylamine (Gamage, S. A.; Spicer, J. A.; Rewcastle, G. W.; Milton, J.; *J. Med. Chem.*, 2002, 45(3), 740-743) following the procedure of Example 67.

m.p. 217.8-219.0°C

δ(CDCl3): 1.48 (t, 3H), 1.58 (s, 3H), 4.34 (q, 2H), 6.82 (dd,1H), 7.35 (m, 7H), 8.22 (s, 1H), 8.38 (s, 1H), 10.22 (s, 1H)

EXAMPLE 143

5-Acetyl-4-[(2-chloropyridin-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained (30%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 2-chloropyridin-3-ylamine following the procedure of Example 63. The product was purified by column cromatography (silica gel, hexane/ethyl acetate 2:1).

m.p. 153.0-153.6°C

δ(CDCl3): 1.43 (t, 3H), 1.81 (s, 3H), 4.30 (q, 2H), 7.22 (m, 1H), 7.39 (m, 6H), 8.45 (m, 1H), 8.2 (s, 1H)

EXAMPLE 144

5-Acetyl-4-[(5-chloropyridin-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

Obtained from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 5-chloropyridin-3-ylamine (Heindl, J., Kessler, H.J., DE2607012) following the procedure of Example 63. The product was purified by preparative HPLC/MS.

LRMS: m/Z 369 $(M+1)^+$

Retention Time: 15.0 min*.

EXAMPLE 145

5-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]nicotinamide

Obtained (54%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 5-amino-nicotinamide (Ueno, Y. *Chemica Scripta* 1984, 24(4-5), 185-7) following the procedure of Example 67.

m.p: 235.8-236.8°C

δ(CDCl3): 1.43 (t, 3H), 1.82 (s, 3H), 4.30 (q, 2H), 5.64 (s,1H); 6.22 (s, 1H), 7.41 (m, 5H), 7.73 (s, 1H), 8.55 (d, 1H), 8.69 (s, 1H), 8.76 (d, 1H)

EXAMPLE 146

5-Acetyl-2-ethyl-4-(1,7-naphthyridin-8-ylamino)-6-phenylpyridazin-3(2H)-one

Obtained from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and [1,7]naphthyridin-8-ylamine (Van den Haak, H.J. W.; Van der Plas, H.C.; Van Veldhuizen, B. Journal of Heterocyclic Chemistry 1981, 18(7), 1349-52.) following the procedure of Example 63. The product was purified by preparative HPLC/MS.

LRMS: m/Z 386 $(M+1)^+$

Retention Time: 10.0 min*.

EXAMPLE 147

2-Ethyl-5-glycoloyl-4-[(2-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

To a 0°C stirred solution of potassium hydroxide (510 mg, 9 mmol) in methanol (15 mL) a solution of the title compound of Example 138 (348 mg, 1 mmol) was added dropwise within 10 min. Then, diacetoxyiodobenzene (644 mg, 2 mmol) was added portionwise

* Chromatografic method B.

and the final mixture was stirred at rt overnight. Solvent was removed under reduced pressure and the residue was suspended in ethyl acetate and washed with saturated NH_4Cl solution and brine. The organic layer was dried and solvent was removed to yield a crude product that was purified by column chromathography (10% yield).

LRMS: m/Z 365 $(M+1)^+$.

Retention Time: 13 min*.

EXAMPLE 148

Methyl 5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino] nicotinate

Obtained (21%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 5-aminonicotinic acid methyl esther (Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chemistry-A European Journal* 2002, 8(5), 1218-1226) following the procedure of Example 63. The product was purified by preparative HPLC/MS.

m.p. 144.6-145.8ºC

δ(CDCl3): 1.44 (t, 3H), 1.77 (s, 3H), 3.94 (s, 3H), 4.29 (q, 2H), 7.43 (m, 5H), 7.92 (s, 1H), 8.54 (d, 1H), 8.85 (s, 1H), 9.05 (d, 1H)

EXAMPLE 149

5-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]nicotinic acid

Obtained from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and 5-aminonicotinic acid (Delarge, *J. Pharmaceutica Acta Helvetiae* (1969), 44(10), 637-43) following the procedure of Example 63. The product was purified by preparative HPLC/MS.

LRMS: m/Z 379 $(M+1)^+$

Retention Time: 12.0 min*

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* Chromatografic method B.

EXAMPLE 150

5-Acetyl-2-ethyl-4-(1,5-naphthyridin-3-ylamino)-6-phenylpyridazin-3(2H)-one

Obtained from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and [1,5]naphthyridin-3-ylamine (Czuba W., Akad, M., Wroclaw, P., *Rocniki Chemii*, 1967, 41(2), 289-297) following the procedure of Example 63. The product was purified by preparative HPLC/MS.

LRMS: m/Z 386 $(M+1)^+$

Retention Time: 13.0 min.

EXAMPLE 151

5-Acetyl-2-ethyl-4-[(8-hydroxy-1,7-naphthyridin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

Obtained (43%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and the title compound of Preparation 67 following the procedure of Example 67.

m.p. 269.5-271.3°C

δ(DMSO-d6): 1.35 (m, 3H), 1.48 (s, 3H), 4.19 (q, 2H), 7.44 (m,6H), 8.59 (s, 1H), 8.75 (d, 1H), 9.28 (s, 1H), 11.66 (s, 1H)

EXAMPLE 152

5-Acetyl-2-ethyl-6-phenyl-4-(thien-2-ylamino)pyridazin-3(2H)-one

To a solution of thiophen-2-ylcarbamic acid *tert*-butyl ester (157 mg, 0.78 mmol) (Binder, D., Habison, G., Noe, C.R., *Synthesis*, 1977, 4, 255-256) in ethyl ether (6.5 ml), 12N chlorhidric acid (2.8 mL) was added. The mixture was stirred for 30 min. and the solvent was removed to yield the deprotected thiophen-2-yl-ammonium chloride. Then a solution of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (150 mg, 0.52 mmol) (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) in ethanol (9 ml) and triethylamine (0.26 ml, 3.6 mmol) were added. The resulting mixture was stirred at

room temperature for 3h. The final product was collected by filtration and washed with diethylether to yield the title compound as a yellow solid (38%).

m.p. 182.6-183.5

δ(DMSO-d6): 1.33 (m, 3H), 1.62 (s, 3H), 4.16 (q, 2H), 6.73 (m,1H), 6.82 (m, 1H), 7.27 (m, 3H), 7.40 (m, 3H), 8.89 (s, 1H)

EXAMPLE 153

5-Acetyl-2-ethyl-6-phenyl-4-[(2-phenylpyridin-3-yl)amino]pyridazin-3(2H)-one

Obtained (46%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, J. Med. Chem. 1997, 40, 1417) and 2-phenylpyridin-3-ylamine (Miller, J.A, Farrell, R.P., *Tetrahedron Lett.,* 1998, 39(36), 6441-6444) following the procedure of Example 67.

m.p. 181.8-182.4°C

δ(DMSO-d6): 1.25 (m, 3H), 1.54 (s, 3H), 4.08 (q, 2H), 7.21 (m, 2H), 7.37 (m, 7H), 7.67 (m, 3H), 8.48 (m, 1H), 8.95 (s, 1H)

EXAMPLE 154

Ethyl {5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino] pyridin-2-yl}acetate

Obtained (30%) from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, J. Med. Chem. 1997, 40, 1417) and 5-aminopyridine-2-carboxylic acid ethyl ester (Cooper, G. H.; Rickard, R. L, *J. Chem. Soc.*, 1971, 19, 3257-3260.) following the procedure of Example 67.

LRMS: m/Z 421 $(M+1)^+$

Retention Time: 14.0 min*.

EXAMPLE 155

5-Acetyl-2-ethyl-4-[(6-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

* Chromatografic method B.

To a stirred solution of the title compound of Example 154 (77 mg, 0.18 mmol) in 2 ml of ethanol, 1M NaOH solution (0.5 ml) was added and the mixture was stirred at rt for 1 hour and at 60°C for 1 h. Then it was let to cool down, acidified to pH 6 and refluxed for 3 days. It was the basified to pH 8 and extracted with dichloromethane. The organic layer was finally washed with water and brine, dried and solvent was removed to yield the title product (20%).

LRMS: m/Z 349 $(M+1)^+$.

Retention Time: 12 min.

EXAMPLE 156-162

156. 5-Acetyl-2-ethyl-4-[(6-hydroxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

157. 5-Acetyl-2-ethyl-4-[(2-fluoropyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

158. 5-Acetyl-4-[(6-chloro-4-methylpyridin-3-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

159. 5-Acetyl-2-ethyl-4-[(3-hydroxypyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

160. 5-Acetyl-2-ethyl-4-[(4-methoxypyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

161. 5-Acetyl-2-ethyl-4-(isoquinolin-8-ylamino)-6-phenylpyridazin-3(2H)-one

162. 5-Acetyl-2-ethyl-6-phenyl-4-(quinolin-7-ylamino)pyridazin-3(2H)-one

The title compounds were sinthesized from 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2H)-one (Dal Piaz, V et al, *J. Med. Chem.* 1997, 40, 1417) and the corresponding amines following the proedure of example 67. The ESI/MS data and HPLC retention times are summarized in Table 25.

Table 25

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
156	351	6.9
157	353	8.3
158	383	9.0
159	351	8.5

160	365	6.5
161	385	6.5
162	385	9.6

EXAMPLE 163

5-Acetyl-4-[(5-chloropyridin-3-yl)amino]-2-ethyl-6-(3-fluorophenyl)pyridazin-3(2H)-one

Obtained as a solid (54%) from the title compound of Preparation 36 and 5-chloro pyridin-3-ylamine (Heindl, J.; Kessler, H.J. DE 2607012) following the procedure of Example 67.

m.p. 146.3-147.3°C.

δ(DMSO-d_3): 1.33 (t, 3H), 1.90 (s, 3H), 4.17 (q, 2H), 7.18 (m, 2H), 7.29 (m, 1H), 7.46 (m, 1H), 7.56 (m, 1H), 8.27 (m, 2H), 9.25 (m, 1H).

EXAMPLE 164

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-methoxypyridin-3-yl)amino]pyridazin-3(2H)-one

Obtained as a solid (90%) from the title compound of Preparation 30 and 2-methoxypyridin-3-ylamine (Hwu, J.R; Wong, F. F.; Shiao, M. J., *J. Org. Chem.,* 1992, 57, 5254-5 following the procedure of Example 67.

m.p. 168.8-169.7°C.

δ($CDCl_3$): 1.44 (t, 3H), 1.71 (s, 3H), 3.97 (s, 3H), 4.29 (q, 2H), 6.87 (m, 1H), 7.10 (m, 2H), 7.27 (m, 1H), 7.39 (m, 2H), 8.00 (m, 1H), 8.22 (s, 1H).

EXAMPLES 165-168

165. 5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

166. 5-Acetyl-4-[(2-chloropyridin-3-yl)amino]-2-ethyl-6-(4-fluorophenyl)pyridazin-3(2H)-one

167. 5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

168. 5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(2-fluoropyridin-3-yl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 30 and the corresponding pyridinylamines following the procedure of Example 93. The ESI/MS data and HPLC retention times are summarized in Table 26.

Table 26

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
165	367	7.4
166	387	8.7
167	367	8.4
168	371	8.9

EXAMPLE 169

5-Acetyl-4-[(2-chloropyridin-3-yl)amino]-2-(cyclopropylmethyl)-6-(4-fluorophenyl)pyridazin-3(2H)-one

Obtained as a solid (20%) from the title compound of Preparation 65 and 2-chloropyridin-3-amine following the procedure of Example 67.

LRMS: m/Z 413 $(M+1)^+$.

Retention Time: 16 min*.

* Chromatografic method B.

δ($CDCl_3$): 0.47 (m, 2H), 0.57 (m, 2H), 1.42 (m, 1H), 1.84 (s, 3H), 4.09 (d, 2H), 7.09 (m, 2H), 7.22 (m, 1H), 7.41 (m, 3H), 8.21 (m, 1H), 8.63 (s, 1H).

EXAMPLE 170

5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(2-methoxypyridin-3-yl)amino]pyridazin-3(2H)-one

Obtained as a solid (66%) from the title compound of Preparation 65 and 2-methoxypyridin-3-ylamine (Hwu, J.R; Wong, F. F.; Shiao, M. J., *J. Org. Chem.*, 1992, 57, 5254-5) following the procedure of Example 67.

m.p. 148.1-148.8°C.

δ($CDCl_3$): 0.46 (m, 2H), 0.57 (m, 2H), 1.43 (m, 1H), 1.73 (s, 3H), 3.96 (s, 3H), 4.10 (d, 2H), 6.85 (m, 1H), 7.09 (m, 2H), 7.27 (m, 1H), 7.38 (m, 2H), 7.99 (m, 1H), 8.22 (s, 1H).

EXAMPLE 171

5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(2-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

Obtained as a solid (23%) from the title compound of Preparation 65 and 2-methylpyridin-3- ylamine (Nantka-Namirski, P.; Kaczmarczyk, C.; Toba, L., *Acta Poloniae Pharmaceutica* 1967, 24, 231-7) following the procedure of Example 67.

LRMS: m/Z 393 $(M+1)^+$.

Retention Time: 14 min.

δ($CDCl_3$): 0.50 (m, 2H), 0.58 (m, 2H), 1.43 (m, 1H), 1.65 (s, 3H), 2.57 (s, 3H), 4.10 (d, 2H), 7.09 (m, 3H), 7.35 (m, 3H), 8.12 (s, 1H), 8.38 (m, 1H).

EXAMPLES 172-174

172. 5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(2-fluoropyridin-3-yl)amino]pyridazin-3(2H)-one

173. 5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

174. 5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-[(pyridin-3-yl) amino]pyridazin-3(2H)-one

The title compounds were synthesized from the title compound of Preparation 65 and the corresponding pyridnylamines following the procedure of Example 93. The ESI/MS data and HPLC retention times are summarized in Table 27.

Table 27

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
172	397	9.2
173	393	9.2
174	379	8.3

EXAMPLES 175-177

175. 5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(2-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

176. 5-Acetyl-6-(3-chlorophenyl)-4-[(2-chloropyridin-3-yl)amino]-2-ethylpyridazin-3(2H)-one

177. 5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

The title compounds were synthesized from 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2H)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417)

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* Chromatografic method B

and the corresponding pyridinylamines following the procedure of Example 93.The ESI/MS data and HPLC retention times are summarized in Table 28.

Table 28

EXAMPLE	ESI/MS m/e $(M+H)^+$	Retention Time (min)
175	383	8.3
176	404	9.3
177	383	9.1

EXAMPLE 178

Methyl 5-[(5-acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino] quinoline-8-carboxylate

A mixture of (160 mg, 0.556 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417), 5-aminoquinoline-8-carboxilic acid methyl ester (226 mg, 1.114 mmol) (Preparation 99)and ethanol (8 mL) was introduced in the microwave oven. The mixture was stirred at 120 °C during 45 minutes. The solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane/methanol 100:1) and preparative HPLC/MS to yield the title compound (7 mg, 3 % yield).

LRMS: m/Z 443 $(M+1)^+$.

Retention time: 13 min*.

EXAMPLE 179

5-Acetyl-2-ethyl-4-[(4-methylpyridin-3-yl)amino]-6-phenylpyridazin-3(2H)-one

A mixture of the title compound of Preparation 49 (2.0 g, 7.77 mmol), 3-bromo-4-methylpyridine (1.8 ml, 15.5 mmol), anhydrous cuprous iodide (100 mg; 0.52 mmol) and potassium carbonate (1.60 g, 11.6 mmol) stirred at 145°C for 12 h. It was let lo

* Chromatografic method B

cool down and was partiotioned between ethyl acetate and water. The organic layer was wshed with water and brine, dried and solvent was removed in vacuo. The solid thus obtained was thoroughly washed with warm ethyl ether and recrystallized from methanol to yield the final product as a cream solid (0.97 g, 34% yield).

m.p. 215.9-216.3°C.

δ(DMSO-d_3): 1.18 (t, 3H), 1.28 (s, 3H), 2.05 (s, 3H), 4.04 (q, 2H), 7.15 (m, 3H), 7.28 (m, 3H), 8.12 (m, 2H), 8.62 (s, 1H).

EXAMPLE 180

5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(4-methoxyphenyl)pyridazin-3(2H)-one

Obtained as a solid (13%) from the title compound of preparation 71 and 4-bromoisoquinoline following the procedure of Example 101.

m.p. 210.8-212.7 °C.

δ(DMSO-d_6): 1.28 (s, 3H), 1.37 (t, 3H), 3.7 (s, 3H), 4.2 (q, 2H), 6.9 (d, 2H), 7.15 (d, 2H), 7.7 (t, 1H), 7.8 (t, 1H), 7.97 (d, 1H), 8.15 (d, 1H), 8.29 (s, 1H), 9.17 (s, 1H).

EXAMPLE 181

5-Acetyl-2-ethyl-6-(4-methoxyphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained as a solid (33%) from the title compound of Preparation 71 and 3-bromopyridine following the procedure of Example 101.

m.p. 175.0-175.7 °C.

δ(DMSO-d_6): 1.3 (t, 3H), 1.7 (s, 3H), 3.8 (s, 3H), 4.16 (q, 2H), 6.97 (d, 2H), 7.23 (d, 2H), 7.27 (m, 1H), 7.43 (d, 1H), 8.27 (bs, 1H), 8.32 (s, 1H), 9.04 (s, 1H, *NH*).

EXAMPLE 182

5-Acetyl-2-ethyl-6-(4-methoxyphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

Obtained as a solid (15%) from the title compound of Preparation 71 and 5-quinolylboronic acid following the procedure of Example 1.

m.p. 233.2-233.9 °C.

δ(DMSO-d_6): 1.33 (s, 3H), 1.37 (t, 3H), 3.74 (s, 3H), 4.21 (q, 2H), 6.91 (d, 2H), 7.16 (d, 2H), 7.35 (d, 1H), 7.55 (m ,1H), 7.60 (m, 1H), 7.86 (d, 1H), 8.41 (d, 1H), 8.92 (m, 1H), 9.13 (s, 1H, *NH*).

EXAMPLE 183

5-Acetyl-2-ethyl-6-(4-methoxy-phenyl)-4-(1-oxy-quinolin-5-ylamino)- -pyridazin-3(2H)-one

A solution of *m*-chloroperbenzoic acid (36.4 mg, 0.16 mmol) in dry dichloromethane (1 mL) was added to a solution of the title compound of Example 182 (70 mg, 0.16 mmol) in 2 mL of dichloromethane and the mixture was stirred at RT under argon overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography (C-18 reverse phase Biotage© cartridge (water (0.1M ammonium acetate)/acetonitrile 99:1 to 1:99) to yield the title complound as a solid (43 mg, 62% yield).

m.p. 259.7-261.3 °C.

δ(DMSO-d_6): 1.37 (t, 3H), 1.43 (s, 3H), 3.75 (s, 3H), 4.20 (q, 2H), 6.94 (d, 2H), 7.18 (d, 2H), 7.48 (m, 2H), 7.66 (t, 1H), 7.95 (d, 1H), 8.37 (d, 1H), 8.61 (d, 1H), 9.19 (s, 1H, *NH*).

EXAMPLE 184

5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(3-methoxyphenyl)pyridazin-3(2H)-one

Obtained as a solid (24%) from the title compound of Preparation 75 and 4-bromoisoquinoline following the procedure of Example 101.

m.p. 190.0-190.5 °C.

δ(DMSO-d_6): 1.28 (s, 3H), 1.38 (t, 3H), 3.70 (s, 3H), 4.22 (q, 2H), 6.77 (s, 1H), 6.79 (d, 1H), 6.95 (d, 1H), 7.28 (t, 1H), 7.71 (t, 1H), 7.82 (t, 1H), 7.97 (d, 1H), 8.15 (d, 1H), 8.30 (s, 1H), 9.17 (s, 1H, *NH*), 9.18 (s, 1H).

EXAMPLE 185

5-Acetyl-2-ethyl-6-(3-methoxyphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained as a solid (33%) from the title compound of Preparation 75 and 3-bromopyridine following the procedure of Example 101.

m.p. 152.7-153.8 °C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.73 (s, 3H), 3.75 (s, 3H), 4.16 (q, 2H), 6.85 (m, 2H), 6.98 (d, 1H), 7.27-731 (m, 2H), 7.42 (d, 1H), 8.27 (m, 1H), 8.32 (s, 1H), 9.08 (s, 1H, *NH*).

EXAMPLE 186

5-Acetyl-2-ethyl-6-(3-methoxyphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

Obtained as a solid (28%) from the title compound of Preparation 75 and 5-quinolylboronic acid following the procedure of Example 1.

m.p. 194.3-195.8 °C.

δ(DMSO-d_6): 1.32 (s, 3H), 1.37 (t, 3H), 3.70 (s, 3H), 4.21 (q, 2H), 6.77 (s, 1H), 6.78 (d, 1H), 6.95 (d, 1H), 7.30 (t, 1H), 7.34 (d, 1H), 7.54-7.63 (m ,2H), 7.86 (d, 1H), 8.42 (d, 1H), 8.92 (m, 1H), 9.18 (s, 1H, *NH*).

EXAMPLE 187

5-Acetyl-2-ethyl-6-(3-methoxyphenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

Obtained as a yellow solid (58%) from the title compound of Example 186 following the procedure of Example 183.

m.p. 215.5-216.1 °C.

δ(DMSO-d_6): 1.37 (t, 3H), 1.43 (s, 3H), 3.71 (s, 3H), 4.21 (q, 2H), 6.80 (s, 1H), 6.81 (d, 1H), 6.96 (d, 1H), 7.30 (t, 1H), 7.48 (m, 2H), 7.66 (t, 1H), 7.95 (d, 1H), 8.37 (d, 1H), 8.61 (d, 1H), 9.24 (s, 1H, *NH*).

EXAMPLE 188

5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(4-methylphenyl)pyridazin-3(2H)-one

Obtained as a solid (18%) from the title compound of Preparation 79 and 4-bromoisoquinoline following the procedure of Example 101.

m.p. 201.7-202.1 °C.

δ(DMSO-d_6): 1.27 (s, 3H), 1.37 (t, 3H), 2.29 (s, 3H), 4.21 (q, 2H), 7.12 (d, 2H), 7.17 (d, 2H), 7.72 (t, 1H), 7.82 (t, 1H), 7.97 (d, 1H), 8.15 (d, 1H), 8.30 (s, 1H), 9.15 (s, 1H, *NH*), 9.17 (s, 1H).

EXAMPLE 189

5-Acetyl-2-ethyl-6-(4-methylphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained as a solid (18%) from the title compound of Preparation 79 and 3-bromopyridine following the procedure of Example 101.

m.p. 187.8-189.1 °C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.72 (s, 3H), 2.32 (s, 3H), 4.17 (q, 2H), 7.20 (q, 4H), 7.27 (m, 1H), 7.43 (d, 1H), 8.26 (d, 1H), 8.32 (s, 1H), 9.05 (s, 1H, *NH*).

EXAMPLE 190

5-Acetyl-2-ethyl-6-(4-methylphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

Obtained as a solid (40%) from the title compound of Preparation 79 and 5-quinolylboronic acid following the procedure of Example 1.

LRMS (m/z): 399 $(M+1)^+$.

Retention Time: 15 min*.

* Chromatografic method B

m.p. 269.8-271.6 °C.

EXAMPLE 191

5-Acetyl-2-ethyl-6-(4-methylphenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

Obtained as a solid (48%) from the title compound of Example 190 following the procedure of Example 183.

m.p. 231.7-232.5 °C.

δ(MeOH-d_4): 1.44 (t, 3H), 1.47 (s, 3H), 2.35 (s, 3H), 4.29 (q, 2H), 7.20 (s, 4H), 7.52 (d, 1H), 7.6 (dd, 1H), 7.80 (t, 1H), 8.35 (d, 1H), 8.53 (d, 1H), 8.72 (d, 1H).

EXAMPLE 192

5-Acetyl-2-ethyl-6-(4-methylphenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

Obtained as a solid (9%) from the title compound of Preparation 79 and 4-methyl-3-bromopyridine following the procedure of Example 101.

m.p. 196.1-197.3 °C.

δ(DMSO-d_6): 1.34 (t, 3H), 1.43 (s, 3H), 2.22 (s, 3H), 2.31 (s, 3H), 4.17 (q, 2H), 7.15 (d, 2H), 7.19 (d, 2H), 7.24 (d, 1H), 8.21 (s, 1H), 8.26 (d, 1H), 8.72 (s, 1H, *NH*).

EXAMPLE 193

5-Acetyl-2-ethyl-4-(isoquinolin-4-ylamino)-6-(3-methylphenyl)pyridazin-3(2H)-one

Obtained as a solid (27%) from the title compound of Preparation 83 and 4-bromoisoquinoline following the procedure of Example 101.

Retention Time: 15 min*.

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* Chromatografic method B

δ(DMSO-d_6): 1.26 (s, 3H), 1.37 (t, 3H), 2.27 (s, 3H), 4.22 (q, 2H), 6.99 (d, 1H), 7.07 (s, 1H), 7.18-7.26 (m, 2H), 7.72 (t, 1H), 7.82 (t, 1H), 7.97 (d, 1H), 8.15 (d, 1H), 8.29 (s, 1H), 9.17 (s, 2H).

EXAMPLE 194

5-Acetyl-2-ethyl-6-(3-methylphenyl)-4-(pyridin-3-ylamino)pyridazin-3(2H)-one

Obtained as a solid (21%) from the title compound of Preparation 83 and 3-bromopyridine following the procedure of Example 101.

m.p. 134.9-136.1 °C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.72 (s, 3H), 2.32 (s, 3H), 4.17 (q, 2H), 7.06 (d, 1H), 7.15 (s, 1H), 7.22-7.31 (m, 3H), 7.43 (dd, 1H), 8.26 (dd, 1H), 8.32 (s, 1H), 9.08 (s, 1H, *NH*).

EXAMPLE 195

5-Acetyl-2-ethyl-6-(3-methylphenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

Obtained as a solid (25%) from the title compound of Preparation 83 and 5-quinolylboronic acid following the procedure of Example 1.

LRMS (m/z): 399 $(M+1)^+$.

Retention Time: 14 min*.

m.p. 245.0-246.1 °C.

EXAMPLE 196

5-acetyl-2-ethyl-6-(3-methylphenyl)-4-[(4-methylpyridin-3-yl)amino]pyridazin-3(2H)-one

Obtained as a solid (24%) from the title compound of Preparation 83 and 4-methyl-3-bromopyridine following the procedure of Example 1.

m.p. 171.1-172.0 °C.

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* Chromatografic method B

δ(DMSO-d_6): 1.34 (t, 3H), 1.43 (s, 3H), 2.22 (s, 3H), 2.30 (s, 3H), 4.18 (q, 2H), 7.02 (d, 1H), 7.10 (s, 1H), 7.20-7.28 (m, 3H), 8.21 (s, 1H), 8.25 (d, 1H), 8.75 (s, 1H, *NH*).

EXAMPLE 197

Methyl 4-[4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazin-3-yl]benzoate

Obtained as a solid (18%) from the title compound of Preparation 88 and 4-bromoisoquinoline following the procedure of Example 101.

m.p. 182.9-183.6 °C.

δ(DMSO-d_6): 1.28 (s, 3H), 1.36 (t, 3H), 3.82 (s, 3H), 4.20 (q, 2H), 7.37 (d, 2H), 7.72 (t, 1H), 7.80 (t, 1H), 7.91 (d, 2H), 7.97 (d, 1H), 8.12 (d, 1H), 8.27 (s, 1H), 9.14 (s, 1H), 9.22 (s, 1H, *NH*).

EXAMPLE 198

Methyl 4-[4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoate

Obtained as a solid (15%) from the title compound of Preparation 88 and 3-bromopyridine following the procedure of Example 101.

δ(DMSO-d_6): 1.3 (t, 3H), 1.7 (s, 3H), 3.82 (s, 3H), 4.20 (q, 2H), 7.27 (m, 1H), 7.44 (d, 3H), 7.97 (d, 2H), 8.27 (d, 1H), 8.32 (s, 1H), 9.18 (s, 1H, *NH*).

LRMS (m/z): 393 $(M+1)^+$.

Retention Time: 13 min*.

* Chromatografic method B

EXAMPLE 199

4-[4-Acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoic acid

Obtained as a solid (46%) from the title compound of Example 198 following the procedure of Example 41.

m.p. 237.5-238.8 °C.

δ(DMSO-d_6): 1.34 (t, 3H), 1.77 (s, 3H), 4.19 (q, 2H), 7.27 (m, 1H), 7.44 (d, 3H), 7.95 (d, 2H), 8.27 (d, 1H), 8.32 (s, 1H), 9.16 (s, 1H, *NH*), 13.09 (s, 1H, *COOH*).

EXAMPLE 200

Methyl 4-{4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazin-3-yl}benzoate

Obtained as a solid (32%) from the title compound of Preparation 88 and 4-methyl-3-bromopyridine following the procedure of Example 101.

m.p. 195.5-197.0 °C.

δ(DMSO-d_6): 1.35 (t, 3H), 1.48 (s, 3H), 2.22 (s, 3H), 3.86 (s, 3H), 4.19 (q, 2H), 7.24 (d, 1H), 7.43 (d, 2H), 7.96 (d, 2H), 8.22 (s, 1H), 8.25 (d, 1H), 8.80 (s, 1H, *NH*).

EXAMPLE 201

4-{4-Acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazin-3-yl}benzoic acid

Obtained as a solid (13%) from the title compound of Example 200 following the procedure of Example 41.

m.p. 242.7-243.3 °C.

δ(DMSO-d_6): 1.35 (t, 3H), 1.48 (s, 3H), 2.22 (s, 3H), 4.19 (q, 2H), 7.24 (d, 1H), 7.40 (d, 2H), 7.96 (d, 2H), 8.22 (s, 1H), 8.25 (d, 1H), 8.80 (s, 1H, *NH*).

EXAMPLE 202

Methyl 3-[4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoate

Obtained as a solid (20%) from the title compound of Preparation 93 and 3-bromopyridine following the procedure of Example 101.

m.p. 148.8-150.2 °C.

δ(MeOH-d_4): 1.33 (t, 3H), 1.68 (s, 3H), 3.82 (s, 3H), 4.19 (q, 2H), 7.27 (m, 1H), 7.44-7.52 (m, 3H), 7.93 (s, 1H), 7.97 (d, 1H), 8.20 (dd, 1H), 8.25 (s, 1H).

EXAMPLE 203

3-[4-Acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazin-3-yl]benzoic acid

Obtained as a solid (42%) from the title compound of Example 202 following the procedure of Example 41.

m.p. 269.1-270.3 °C.

δ(DMSO-d_6): 1.34 (t, 3H), 1.75 (s, 3H), 4.19 (q, 2H), 7.27 (m, 1H), 7.44-7.51 (m, 2H), 7.54 (s, 1H), 7.89 (s, 1H), 7.97 (d, 1H), 8.27 (s, 1H), 8.35 (s, 1H), 9.13 (s, 1H, *NH*), 13.13 (s, 1H, *COOH*).

EXAMPLE 204

5-Acetyl-4-[(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (12%) from the title compound of Preparation 16 and 3-chloro-4-fluoro-boronic acid following the procedure of Example 1.

m.p. 168.6-169.6 °C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.85 (s, 3H), 4.18 (q, 2H), 7.08 (m, 1H), 7.29-7.35 (m, 4H), 8.60 (d, 2H), 9.19 (s, 1H, *NH*).

EXAMPLE 205

5-Acetyl-4-[bis(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-4-ylpyridazin-3(2H)-one

Obtained as a solid (4%) from the title compound of Preparation 16 and an exces of 3-chloro-4-fluoro-boronic acid following the procedure of Example 1.

m.p. 155.7-156.2 °C.

δ(DMSO-d_6): 1.33 (t, 3H), 2.18 (s, 3H), 4.16 (q, 2H), 7.06 (m, 2H), 7.31-7.41 (m, 6H), 8.65 (bs, 2H).

EXAMPLE 206

5-Acetyl-4-[(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

Obtained as a solid (10%) from the title compound of Preparation 14 and 3-chloro-4-fluoro-boronic acid following the procedure of Example 1.

m.p. 159.8-160.3 °C.

δ(DMSO-d_6): 1.34 (t, 3H), 1.82 (s, 3H), 4.18 (q, 2H), 7.08 (m, 1H), 7.29-7.35 (m, 3H), 7.43 (bs, 1H), 7.73 (d, 1H), 8.61 (bs, 1H), 9.18 (s, 1H, *NH*).

EXAMPLE 207

5-Acetyl-4-[bis(3-chloro-4-fluorophenyl)amino]-2-ethyl-6-pyridin-3-ylpyridazin-3(2H)-one

Obtained as a solid (11%) from the title compound of Preparation 14 and 3-chloro-4-fluoro-boronic acid following the procedure of Example 1.

δ(DMSO-d_6): 1.33 (t, 3H), 2.14 (s, 3H), 4.16 (q, 2H), 7.06 (m, 2H), 7.32-7.38 (m, 4H), 7.48 (bs, 1H), 7.80 (d, 1H), 8.61 (bs, 2H).

LRMS (m/z): 515 $(M+1)^+$.

Retention Time: 18 min*.

* Chromaotgrafic method B.

EXAMPLE 208

Methyl [4-acetyl-6-oxo-3-phenyl-5-(quinolin-5-ylamino)pyridazin-1(6H)-yl]acetate

Obtained as a solid (44%) from the title compound of Preparation 95 and quinoline-5-boronic acid following the procedure of Example 1.

m.p. 193.6-194.3°C.

$\delta(CDCl_3)$: 1.40 (s, 3H), 3.80 (s, 3H), 4.98 (s, 2H), 7.32 (m, 6H), 7.48 (m, 1H), 7.62 (m, 1H), 8.06 (m, 1H), 8.41 (m,2H), 8.98 (m, 1H).

EXAMPLE 209

[4-Acetyl-6-oxo-3-phenyl-5-(quinolin-5-ylamino)pyridazin-1(6H)-yl]acetic acid

Obtained from the title compound of Example 208 following the procedure of Example 41.

LRMS: m/Z 415 $(M+1)^+$.

Retention Time: 7.7 min

EXAMPLE 210

5-Acetyl-2-ethyl-4-[(3-methylpyridin-2-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 2-amino-3-methylpyridine (45 mg, 0.417 mmol) was added portionwise. The resulting mixture was stirred at room temperature for five days. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 2:1) to yield the title compound (26 mg, 27% yield).

$\delta(DMSO\text{-}d_6)$: 1.35 (t, 3H), 1.80 (s, 3H), 2.32 (s, 3H), 4.22 (q, 2H), 6.95 (m, 1H), 7.35 (m, 2H), 7.47 (m, 3H), 7.60 (d, 1H), 7.95 (d, 1H), 8.50 (s, 1H).

EXAMPLE 211

5-Acetyl-2-ethyl-6-phenyl-4-(1H-pyrazol-3-ylamino)pyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL) under nitrogen atmosphere, 3-aminopyrazol (35 mg, 0.417 mmol) was added. The resulting mixture was stirred at room temperature during 30 minutes and the final product was collected by filtration and washed with diethylether to yield the title compound (50 mg, 55.7 % yield).

δ(DMSO-d_6): 1.29 (t, 3H), 1.55 (s, 3H), 4.15 (q, 2H), 5.73 (s, 1H), 7.14 (s, 1H), 7.38-7.52 (m, 6H), 10.80 (s, 1H).

EXAMPLE 212

5-Acetyl-2-ethyl-6-phenyl-4-(9H-purin-6-ylamino)pyridazin-3(2H)-one

To a stirred solution of 250 mg (0.870 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (12 mL), adenine (235 mg, 1.740 mmol) was added. The resulting mixture was stirred and refluxed during two days. The solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane/methanol 95:5) and preparative HPLC/MS to yield the title compound (4.4 mg, 1.4% yield).

LRMS: m/Z 376 $(M+1)^+$.

Retention time: 7.5 min.

EXAMPLE 213

5-Acetyl-2-ethyl-4-[(3-methylisoxazol-5-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 200 mg (0.696 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (10 mL), 5-amino-3-methylisoxazole (204 mg, 2.088 mmol) was added. The resulting mixture was stirred at 50 °C for four days. The solvent was evaporated and

the residue purified by column chromatography (silica gel, hexane/ethyl acetate 2:1) to yield the title compound (35 mg, 14.9% yield).

m.p. 177.6-178.7 °C

δ(DMSO-d_6): 1.33 (t, 3H), 1.82 (s, 3H), 2.13 (s, 3H), 4.19 (q, 2H), 5.71 (s, 1H), 7.34 (m, 2H), 7.47 (m, 3H), 10.02 (s, 1H).

EXAMPLE 214

5-Acetyl-2-ethyl-4-[(8-hydroxyquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 5-amino-8-quinolinol (67 mg, 0.417 mmol) was added. The resulting mixture was stirred at room temperature during 40 hours and the final product was collected by filtration and washed with diethylether to yield the title compound (100 mg, 90 % yield).

m.p. 261.9-262.6 °C.

δ(DMSO-d_6): 1.25 (s, 3H), 1.37 (t, 3H), 4.20 (q, 2H), 6.90 (d, 1H), 7.22-7.36 (m, 6H), 7.60 (m, 1H), 8.30 (d, 1H), 8.80 (m, 2H), 9.97 (s, 1H).

EXAMPLE 215

5-Acetyl-2-ethyl-4-(1H-indazol-7-ylamino)-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 1H-indazol-7-amine (56 mg, 0.417 mmol) was added. The resulting mixture was stirred at room temperature during one hour and the final product was collected by filtration and washed with diethylether to yield the title compound (90 mg, 86.5 % yield).

m.p. 262.6-263.8 °C.

δ(DMSO-d_6): 1.12 (s, 3H), 1.37 (t, 3H), 4.20 (q, 2H), 7.03 (m, 2H), 7.25 (m, 2H), 7.38 (m, 3H), 7.57 (m, 1H), 8.06 (s, 1H), 9.04 (s, 1H), 13.08(s, 1H).

EXAMPLE 216

5-Acetyl-4-[(6-bromoquinolin-8-yl)amino]-2-ethyl-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.279 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 8-amino-6-bromoquinoline (93 mg, 0.417 mmol) was added. The resulting mixture was stirred at room temperature or one day. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 3:1) to yield the title compound (110 mg, 85.3% yield).

m.p. 146.8-147.5 °C

δ(DMSO-d_6): 1.35 (t, 3H), 1.76 (s, 3H), 4.21 (q, 2H), 7.27 (s, 1H), 7.40-7.48 (m, 5H), 7.65 (m,1H), 7.91 (s, 1H), 8.36 (d, 1H), 8.93 (m, 1H), 9.36 (s, 1H).

EXAMPLE 217

5-Acetyl-2-ethyl-4-[(5-methylisoxazol-3-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 3-amino-5-methylisoxazol (96 mg, 0.978 mmol) was added. The resulting mixture was stirred at room temperature for four days and the final product was collected by filtration and washed with diethylether to yield the title compound (35 mg, 37.2 % yield).

m.p. 170.1-170.8 °C.

δ(DMSO-d_6): 1.33 (t, 3H), 1.82 (s, 3H), 2.32 (s, 3H), 4.19 (q, 2H), 6.12 (s, 1H), 7.32 (m, 2H), 7.45 (m, 3H), 9.36 (s, 1H).

EXAMPLE 218

5-Acetyl-2-ethyl-4-(isoxazol-3-ylamino)-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 3-aminoisoxazol (70 mg, 0.834 mmol) was added. The resulting

mixture was stirred at room temperature for four days and the final product was collected by filtration and washed with diethylether to yield the title compound (58 mg, 63.7 % yield).

m.p. 176.4-177.1 °C.

δ(DMSO-d_6): 1.34 (t, 3H), 1.84 (s, 3H), 4.20 (q, 2H), 6.43 (s, 1H), 7.32 (m, 2H), 7.46 (m, 3H), 8.67 (s, 1H), 9.45 (s, 1H).

EXAMPLE 219

5-Acetyl-2-(cyclopropylmethyl)-6-phenyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.319 mmol) of Preparation 97 in ethanol (4 mL), 5-aminoquinoline (69 mg, 0.479 mmol) was added. The resulting mixture was stirred at room temperature during one day and the final product was collected by filtration and washed with diethylether to yield the title compound (53 mg, 40.4 % yield).

m.p. 203.9-205.1 °C.

δ(DMSO-d_6): 0.46 (m, 2H), 0.55 (m, 2H), 1.33 (m, 4H), 4.06 (q, 2H), 7.24 (m, 2H), 7.35 (m, 4H), 7.58 (m, 2H), 7.86 (d, 1H), 8.44 (d, 1H), 8.93 (m, 1H), 9.21 (s, 1H).

EXAMPLE 220

5-Acetyl-2-(cyclopropylmethyl)-6-phenyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.319 mmol) of the title compound of Preparation 97 in ethanol (4 mL), 8-aminoquinoline (69 mg, 0.479 mmol) was added. The resulting mixture was stirred at room temperature during 22 hours. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 3:1) to yield the title compound (110 mg, 84.6% yield).

m.p. 123.1-124.7 °C.

δ(DMSO-d_6): 0.45 (m, 2H), 0.53 (m, 2H), 1.30 (m, 1H), 1.61 (s, 3H), 4.05 (q, 2H), 7.24 (d, 1H), 7.37-7.49 (m, 6H), 7.61 (m, 1H), 7.71 (d, 1H), 8.40 (d, 1H), 8.93 (m, 1H), 9.35 (s, 1H).

EXAMPLE 221

5-Acetyl-2-ethyl-4-[(1-methyl-1H-pyrazol-3-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 80 mg (0.278 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 3-amino-1-methylpyrazol (40 mg, 0.417 mmol) was added. The resulting mixture was stirred at room temperature during three hours and the final product was collected by filtration and washed with diethylether to yield the title compound (56 mg, 59.6 % yield).

m.p. 202.8-203.9 °C.

δ(DMSO-d_6): 1.32 (t, 3H), 1.72 (s, 3H), 3.62 (s, 3H), 4.16 (q, 2H), 5.94 (m, 1H), 7.29 (m, 2H), 7.43 (m, 3H), 7.52 (s, 1H), 8.84 (s, 1H).

EXAMPLE 222

5-Acetyl-2-ethyl-4-[(1-oxidoquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

A solution of the compound synthesized in Example 82 (210 mg, 0.546 mmol) in dichloromethane (3 mL) was added dropwise to a cold solution of 3-chloroperoxybenzoic acid (111 mg, 0.546 mmol) in dichloromethane (7 mL). The mixture was stirred at room temperature for 27 hours and added to a solution of $KHSO_4$ in water (20 mL, 25%).The organic layer was washed with water, dried over sodium sulfate anhydride and evaporated.

The crude obtained was purified by column chromatography (silica gel, dichloromethane/methanol 110:5) to yield 160 mg (0.399 mmol) of the title compound (73%).

m.p. 264.0-264.8 °C.

δ (DMSO-d_6): 1,37 (t, 3H), 1.41 (s, 3H), 4.21 (q, 2H), 7.26 (bs, 2H), 7.39 (bs, 3H), 7.48 (m, 2H), 7.65 (m, 1H), 7.96 (d, 1H), 8.35 (d, 1H), 8.61 (m, 1H), 9.24 (s, 1H).

EXAMPLE 223

5-Acetyl-2-ethyl-4-[(2-oxidoisoquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

The title compound was synthesized from the title compound of Example 84 following the procedure of Example 222.The crude obtained was purified by preparative HPLC/MS to yield the title compound (24 % yield).

LRMS: m/Z 401 $(M+1)^+$.

Retention time: 7.3 min.

EXAMPLE 224

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.311 mmol) of 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (5 mL), 5-aminoquinoline (67 mg, 0.467 mmol) was added. The resulting mixture was stirred at room temperature during two hours and the final product was collected by filtration and washed with diethylether to yield the title compound (67 mg, 51.5 % yield).

m.p. 186.2-186.9 °C.

δ(DMSO-d_6): 1.37 (m, 6H), 4.22 (q, 2H), 7.17 (d, 1H), 7.33-7.45 (m, 4H), 7.60 (m, 2H), 7.87 (d, 1H), 8.44 (d, 1H), 8.93 (m, 1H), 9.28 (s, 1H).

EXAMPLE 225

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-(quinolin-8-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.311 mmol) of 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 8-aminoquinoline (67 mg, 0.467 mmol) was added. The resulting mixture was stirred at room temperature for two hours. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 2:1) to yield the title compound (65 mg, 50 % yield).

m.p. 127.0-127.7 °C

δ(DMSO-d_6): 1.36 (t, 3H), 1.65 (s, 3H), 4.22 (q, 2H), 7.27 (m, 2H), 7.41-7.51 (m, 4H), 7.62 (m, 1H), 7.72 (d, 1H), 8.42 (d, 1H), 8.93 (m, 1H), 9.36 (s, 1H).

EXAMPLE 226

5-Acetyl-2-ethyl-6-pyridin-4-yl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

The title compound was synthesized from the title compound of Preparation16 and the corresponding boronic acid following the procedure of Example 1. The resulting residue was purified by column chromatography (silica gel, dichloromethane/methanol 96:4) to yield the title compound (62.6 % yield).

m.p. 214.0-215.5 °C

δ(DMSO-d_6): 1.38 (m, 6H), 4.23 (q, 2H), 7.26 (m, 2H), 7.34 (d,1H), 7.58 (m, 2H), 7.86 (d, 1H), 8.50 (d, 1H), 8.56 (m,2H), 8.92 (m, 1H), 9.35 (s, 1H).

EXAMPLE 227

5-Acetyl-2-ethyl-6-pyridin-3-yl-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

The title compound was synthesized from the title compound of Preparation 14 and the corresponding boronic acid following the procedure of Example 1. The resulting residue was purified by column chromatography (silica gel, dichloromethane/methanol 97:3) to yield the title compound (32 % yield).

m.p. 180.7-181.6 °C

δ(DMSO-d_6): 1.38 (m, 6H), 4.23 (q, 2H), 7.33-7.41 (m, 2H), 7.56-7.67 (m, 3H), 7.87 (d, 1H), 8.46 (m, 2H), 8.56 (m, 1H), 8.93 (m, 1H), 9.32 (s, 1H).

EXAMPLE 228

5-Acetyl-2-ethyl-4-[(8-fluoroquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 150 mg (0.522 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (8 mL), 5-amino-8-fluoroquinoline (127 mg, 0.783 mmol) (Lee, Jae Keun et al.,

Bull. Korean Chem. Soc., 1996, 17(1), 90) was added. The resulting mixture was stirred at room temperature for five hours. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 3:1) to yield the title compound (140 mg, 66.7% yield).

m.p. 245.7-246-6 °C

δ(DMSO-d_6): 1.36 (m, 6H), 4.22 (q, 2H), 7.23 (m, 2H), 7.37-7.47 (m, 5H), 7.70 (m,1H), 8.43 (d, 1H), 8.99 (m, 1H), 9.16 (s, 1H).

EXAMPLE 229

5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-(quinolin-8-ylamino) pyridazin-3(2H)-one

To a stirred solution of 150 mg (0.453 mmol) of the title compound of Preparation 65 in ethanol (8 mL), 8-aminoquinoline (98 mg, 0.680 mmol) was added. The resulting mixture was stirred at room temperature during four hours and the final product was collected by filtration and washed with diethylether to yield the title compound (115 mg, 59.3 % yield).

m.p. 149.7-150.6 °C.

δ(DMSO-d_6): 0.44 (m, 2H), 0.53 (m, 2H), 1.35 (m, 1H), 1.63 (s, 3H), 4.05 (q, 2H), 7.27 (m, 3H), 7.38 (m, 2H), 7.45 (m, 1H), 7.61 (m, 1H), 7.70 (d, 1H), 8.40 (d, 1H), 8.93 (m, 1H), 9.35 (s, 1H).

EXAMPLE 230

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

To a stirred solution of 150 mg (0.491 mmol) of the title compound of Preparation 30 in ethanol (8 mL), 5-aminoquinoline (106 mg, 0.737 mmol) was added. The resulting mixture was stirred at room temperature during two hours and the final product was collected by filtration and washed with diethylether to yield the title compound (140 mg, 70.7 % yield).

m.p. 217.5-218.3 °C

δ(DMSO-d_6): 1.37 (m, 6H), 4.21 (q, 2H), 7.17-7.36 (m, 5H), 7.58 (m, 2H), 7.87 (d,1H), 8.43 (d, 1H), 8.92 (m, 1H), 9.23 (s, 1H).

EXAMPLE 231

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-(quinolin-8-ylamino)pyridazin-3(2H)-one

To a stirred solution of 150 mg (0.491 mmol) of the title compound of Preparation 30 in ethanol (8 mL), 8-aminoquinoline (106 mg, 0.737 mmol) was added. The resulting mixture was stirred at room temperature during one hour and the final product was collected by filtration and washed with diethylether to yield the title compound (130 mg, 65.6 % yield).

m.p. 153.5-154.3 °C

δ(DMSO-d_6): 1.36 (t, 3H), 1.62 (s, 3H), 4.21 (q, 2H), 7.26 (m, 3H), 7.38-7.51 (m, 3H), 7.61 (m, 1H), 7.70 (d, 1H), 8.40 (d, 1H), 8.92 (m, 1H), 9.35 (s, 1H).

EXAMPLE 232

5-Acetyl-2-(cyclopropylmethyl)-6-(4-fluorophenyl)-4-(quinolin-5-ylamino) pyridazin-3(2H)-one

To a stirred solution of 150 mg (0.453 mmol) of the title compound of Preparation 30 in ethanol (8 mL), 5-aminoquinoline (98 mg, 0.680 mmol) was added. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to yield the title compound (174 mg, 89.7% yield).

m.p. 169.2-170.0 °C

δ(DMSO-d_6): 0.45 (m, 2H), 0.55 (m, 2H), 1.36 (m, 4H), 4.05 (q, 2H), 7.18-7.37 (m, 5H), 7.55-7.64 (m, 2H), 7.87 (d, 1H), 8.43 (d, 1H), .92 (m, 1H), 9.23 (s, 1H).

EXAMPLE 233

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

The title compound was synthesized from the title compound of Example 224 (390 mg, 0.931 mmol) following the procedure of Example 222. The crude obtained was

purified by column chromatography (silica gel, dichloromethane/methanol 160:5) to yield the title compound (300 mg, 74.1 % yield).

m.p. 244.0-244.9 °C

δ(DMSO-d_6): 1.37 (t, 3H), 1.48 (s, 3H), 4.21 (q, 2H), 7.19 (d, 1H), 7.35-7.52 (m, 5H), 7.66 (t, 1H), 7.96 (d, 1H), 8.36 (d, 1H), 8.61 (d, 1H), 9.32 (s, 1H).

EXAMPLE 234

5-Acetyl-2-ethyl-4-[(2-methylquinolin-5-yl)amino]-6-phenylpyridazin-3(2H)-one

To a stirred solution of 100 mg (0.348 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (5 mL), 5-amino-2-methylquinoline (83 mg, 0.522 mmol) was added. The resulting mixture was stirred at room temperature during three hours and the final product was collected by filtration and washed with diethylether to yield the title compound (80 mg, 57.6 % yield).

m.p. 204.5-205.1 °C

δ(DMSO-d_6): 1.30 (s, 3H), 1.37 (t, 3H), 2.66 (s, 3H), 4.21 (q, 2H), 7.25 (m, 3H), 7.36 (m, 3H), 7.45 (d, 1H), 7.54 (t, 1H), 7.76 (d, 1H), 8.30 (d, 1H), 9.16 (s, 1H).

EXAMPLE 235

5-Acetyl-6-(3-chlorophenyl)-2-ethyl-4-(isoquinolin-5-ylamino)pyridazin-3(2H)-one

To a stirred solution of 100 mg (0.311 mmol) of 5-acetyl-2-ethyl-4-nitro-6-(3-chlorophenyl)pyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417) in ethanol (4 mL), 5-amino-isoquinoline (67 mg, 0.467 mmol) was added. The resulting mixture was stirred at room temperature for two hours. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexane/ethyl acetate 1:2) to yield the title compound (28 mg, 21.5 % yield).

m.p. 189.2-190.6 °C

δ(DMSO-d_6): 1.37 (m, 6H), 4.22 (q, 2H), 7.18 (d, 1H), 7.34-7.58 (m, 5H), 7.86 (d, 1H), 7.99 (d, 1H), 8.54 (d, 1H), 9.25 (s, 1H), 9.33 (s, 1H).

EXAMPLE 236

5-Acetyl-2-ethyl-6-(4-fluorophenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

The title compound was synthesized from the title compound of Example 230 (430 mg, 1.069 mmol) following the procedure of Example 222. The crude obtained was purified by column chromatography (silica gel, dichloromethane/methanol 110:5) to yield the title compound (360 mg, 80.5 % yield).

m.p. 245.1-246.0 °C

δ(DMSO-d_6): 1.37 (t, 3H), 1.44 (s, 3H), 4.21 (q, 2H), 7.20-7.31 (m, 4H), 7.46-7.50 (m, 2H), 7.64 (m, 1H), 7.98 (d, 1H), 8.36 (d, 1H), 8.62 (d, 1H), 9.28 (s, 1H).

EXAMPLE 237

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-(quinolin-5-ylamino)pyridazin-3(2H)-one

To a stirred solution of 400 mg (1.31 mmol) of the title compound of Preparation 36 in ethanol (20 mL), 5-aminoquinoline (283 mg, 1.965 mmol) was added. The resulting mixture was stirred at room temperature during two hours and the final product was collected by filtration and washed with diethylether to yield the title compound (320 mg, 60.7 % yield).

m.p. 205.3-206.7 °C

δ(DMSO-d_6): 1.38 (m, 6H), 4.20 (q, 2H), 7.10 (m, 2H), 7.22 (m, 1H), 7.35 (m, 2H), 7.60 (m, 2H), 7.85 (d, 1H), 8.42 (d, 1H), 8.95 (m, 1H), 9.25 (s, 1H).

EXAMPLE 238

5-Acetyl-2-ethyl-6-(3-fluorophenyl)-4-[(1-oxidoquinolin-5-yl)amino]pyridazin-3(2H)-one

The title compound was synthesized from the title compound of Example 237 (200 mg, 0.497 mmol) following the procedure of Example 222. The crude obtained was purified by column chromatography (silica gel, dichloromethane/methanol 200:5) to yield the title compound (150 mg, 72.1 % yield).

m.p. 249.4-250.6 °C

δ(DMSO-d_6): 1.23 (t, 3H), 1.33 (s, 3H), 4.07 (q, 2H), 6.92-7.00 (m, 2H), 7.11 (m, 1H), 7.25-7.38 (m, 3H), 7.51 (m, 1H), 7.82 (d, 1H), 8.22 (d, 1H), 8.48 (d, 1H), 9.17 (s, 1H).

EXAMPLE 239

5-[(5-Acetyl-2-ethyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)amino]quinoline-8-carboxylic acid

A mixture of (160 mg, 0.556 mmol) of 5-acetyl-2-ethyl-4-nitro-6-phenylpyridazin-3(2*H*)-one (Dal Piaz, V *et al*, *J. Med. Chem.* 1997, *40*, 1417), 5-aminoquinoline-8-carboxilic acid (210 mg, 1.114 mmol) (Breckenridge, J. G. et al. *Canadian J.of Research Sect. B*, 1947, 25, 49) and ethanol (8 mL) was introduced in the microwave. The mixture was stirred at 120 °C during 45 minutes. The solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane/methanol 300:1) to yield the title compound (50 mg, 41.7 % yield).

LRMS: m/Z 429 $(M+1)^+$.

Retention time: 14 min*.

The following examples illustrate pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLES:

COMPOSITION EXAMPLE 1

Preparation of tablets

Formulation:

Compound of the present invention	5.0 mg
Lactose	113.6 mg
Microcrystalline cellulose	28.4 mg
Light silicic anhydride	1.5 mg
Magnesium stearate	1.5 mg

* Chromatografic method B

Using a mixer machine, 15 g of the compound of the present invention are mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture is subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material is pulverised using a hammer mill, and the pulverised material is screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate are added to the screened material and mixed. The mixed product is subjected to a tablet making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

COMPOSITION EXAMPLE 2

Preparation of coated tablets

Formulation:

Compound of the present invention	5.0 mg
Lactose	95.2 mg
Corn starch	40.8 mg
Polyvinylpyrrolidone K25	7.5 mg
Magnesium stearate	1.5 mg
Hydroxypropylcellulose	2.3 mg
Polyethylene glycol 6000	0.4 mg
Titanium dioxide	1.1 mg
Purified talc	0.7 mg

Using a fluidised bed granulating machine, 15 g of the compound of the present invention are mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of polyvinylpyrrolidone is dissolved in 127.5 g of water to prepare a binding solution. Using a fluidised bed granulating machine, the binding solution is sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate is added to the obtained granulates and mixed. The obtained mixture is subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution is prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above are coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

COMPOSITION EXAMPLE 3

Preparation of capsules

Formulation:

Compound of the present invention	5.0 mg
Lactose monohydrate	200 mg
Colloidal silicon dioxide	2 mg
Corn starch	20 mg
Magnesium stearate	4 mg

25 g of active compound, 1 Kg of lactose monohydrate, 10 g of colloidal silicon dioxide, 100 g of corn starch and 20 g of magnesium stearate are mixed. The mixture is sieved through a 60 mesh sieve, and then filled into 5,000 gelatine capsules.

COMPOSITION EXAMPLE 4

Preparation of a cream

Formulation:

Compound of the present invention	1 %
Cetyl alcohol	3 %
Stearyl alcohol	4 %
Gliceryl monostearate	4 %
Sorbitan monostearate	0.8 %
Sorbitan monostearate POE	0.8 %
Liquid vaseline	5 %
Methylparaben	0.18 %
Propylparaben	0.02 %
Glycerine	15 %
Purified water csp.	100 %

An oil-in-water emulsion cream is prepared with the ingredients listed above, using conventional methods.